EXHIBIT 8

AMENDED NOTICE OF DEPOSITION BY WRITTEN QUESTIONS TO CUMBERLAND VALLEY SURGERY CENTER ("CVSC")

PK LAW

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February 22, 2016

Sent Via Electronic Mail
April Hitzelberger, Esquire
Waranch & Brown, LLC
1301 York Road, Suite 300
Lutherville, Maryland 21093

Re: NECC MDL – Case No. 1:13-md-2419 (D. Mass.)

Dear Counsel:

In follow-up from our previous letters dated October, 2015 and February 17, 2016 regarding the above litigation, please find attached the following materials for the Deposition by Written Question of your facility's designated 30(b)(6) witness:

1. Second Amended Notice of Deposition;

Please note that the following materials were previously provided, have also been provided again here for your convenience.

1. A copy of Rule 31 of the Federal Rules of Civil Procedure;
2. A copy of written deposition questions for direct examination submitted by the Box Hill Defendants;
3. A copy of written deposition questions for cross-examination submitted by the Plaintiff's Steering Committee

Your facility representative, **Faye Mentor** may bring these items with her to the deposition. Your deposition has been scheduled for **February 25, 2016** at **11:00 AM EST**, to take place at **Cumberland Valley Surgery Center, 1110 Professional Court, #100, Hagerstown, Maryland 21740.** We will arrange to have a court reporter with experience conducting a deposition by written question present.

We anticipate that the format of the deposition will be as follows: At the date and time above, a court reporter will meet your facility's designated 30(b)(6) witness at the location above to conduct the deposition. At all times your facility has the right to have its attorney present for this deposition.

After the witness is sworn in by the court reporter, the court reporter will read aloud the questions submitted by the Box Hill Surgery Center Defendants for direct examination, to which the witness will answer orally. Then the court reporter will read aloud the questions submitted by the Plaintiff Steering Committee for cross-examination, to which the witness will answer orally. The facility representative will be required to answer only the written questions as appear. Once all questions have been read and responded to, the deposition will conclude.

Please contact attorney Gregory Kirby at Pessin Katz & Law, P.A., with any questions or concerns. My contact information is as follows:

Gregory Kirby, Esquire
Pessin Katz Law, P.A.
901 Dulaney Valley Road, Suite 500
Towson, Maryland 21204
(410)938-8800
gkirby@pklaw.com

Thank you for your assistance with this matter.

Sincerely,

Greg Kirby, to

Gregory K. Kirby

cc: Jessica Meeder, Esquire w/enclosures
Discovery Litigation w/enclosures
All other counsel notified via ECF

(i) offer copies to be marked, attached to the deposition, and then used as originals — after giving all parties a fair opportunity to verify the copies by comparing them with the originals; or

(ii) give all parties a fair opportunity to inspect and copy the originals after they are marked — in which event the originals may be used as if attached to the deposition.

(B) Order Regarding the Originals. Any party may move for an order that the originals be attached to the deposition pending final disposition of the case.

(3) Copies of the Transcript or Recording. Unless otherwise stipulated or ordered by the court, the officer must retain the stenographic notes of a deposition taken stenographically or a copy of the recording of a deposition taken by another method. When paid reasonable charges, the officer must furnish a copy of the transcript or recording to any party or the deponent.

(4) Notice of Filing. A party who files the deposition must promptly notify all other parties of the filing.

(g) Failure to Attend a Deposition or Serve a Subpoena; Expenses. A party who, expecting a deposition to be taken, attends in person or by an attorney may recover reasonable expenses for attending, including attorney's fees, if the noticing party failed to:

(1) attend and proceed with the deposition; or

(2) serve a subpoena on a nonparty deponent, who consequently did not attend.

Note. Amended effective December 1, 2015, unless disapproved by Congress (material added in 2015 amendments is indicated by underlining; material deleted by striking out and brackets).

RULE 31. DEPOSITIONS UPON WRITTEN QUESTIONS

(a) When a Deposition May Be Taken.

(1) Without Leave. A party may, by written questions, depose any person, including a party, without leave of court except as provided in Rule 31(a)(2). The deponent's attendance may be compelled by subpoena under Rule 45.

(2) With Leave. A party must obtain leave of court, and the court must grant leave to the extent consistent with Rule 26(b)(1) and (2):

(A) if the parties have not stipulated to the deposition and:

(i) the deposition would result in more than 10 depositions being taken under this rule or Rule 30 by the plaintiffs, or by the defendants, or by the third-party defendants;

(ii) the deponent has already been deposed in the case; or

(iii) the party seeks to take a deposition before the time specified in Rule 26(d); or

(B) if the deponent is confined in prison.

(3) Service; Required Notice. A party who wants to depose a person by written questions must serve them on every other party, with a notice stating, if known, the deponent's name and address. If the name is unknown, the notice must provide a general description sufficient to identify the person or the particular class or group to which the person belongs. The notice must also state the name or descriptive title and the address of the officer before whom the deposition will be taken.

(4) Questions Directed to an Organization. A public or private corporation, a partnership, an association, or a governmental agency may be deposed by written questions in accordance with Rule 30(b)(6).

(5) Questions from Other Parties. Any questions to the deponent from other parties must be served on all parties as follows: cross-questions, within 14 days

after being served with the notice and direct questions; redirect questions, within 7 days after being served with cross-questions; and recross-questions, within 7 days after being served with redirect questions. The court may, for good cause, extend or shorten these times.

(b) Delivery to the Officer; Officer's Duties. The party who noticed the deposition must deliver to the officer a copy of all the questions served and of the notice. The officer must promptly proceed in the manner provided in Rule 30(c), (e), and (f) to:

(1) take the deponent's testimony in response to the questions;

(2) prepare and certify the deposition; and

(3) send it to the party, attaching a copy of the questions and of the notice.

(c) Notice of Completion or Filing.

(1) Completion. The party who noticed the deposition must notify all other parties when it is completed.

(2) Filing. A party who files the deposition must promptly notify all other parties of the filing.

Note. Amended effective December 1, 2015, unless disapproved by Congress (material added in 2015 amendments is indicated by underlining; material deleted by striking out and brackets).

RULE 32. USING DEPOSITIONS IN COURT PROCEEDINGS

(a) Using Depositions.

(1) In General. At a hearing or trial, all or part of a deposition may be used against a party on these conditions:

(A) the party was present or represented at the taking of the deposition or had reasonable notice of it;

(B) it is used to the extent it would be admissible under the Federal Rules of Evidence if the deponent were present and testifying; and

(C) the use is allowed by Rule 32(a)(2) through (8).

(2) Impeachment and Other Uses. Any party may use a deposition to contradict or impeach the testimony given by the deponent as a witness, or for any other purpose allowed by the Federal Rules of Evidence.

(3) Deposition of Party, Agent, or Designee. An adverse party may use for any purpose the deposition of a party or anyone who, when deposed, was the party's officer, director, managing agent, or designee under Rule 30(b)(6) or 31(a)(4).

(4) Unavailable Witness. A party may use for any purpose the deposition of a witness, whether or not a party, if the court finds:

(A) that the witness is dead;

(B) that the witness is more than 100 miles from the place of hearing or trial or is outside the United States, unless it appears that the witness's absence was procured by the party offering the deposition;

(C) that the witness cannot attend or testify because of age, illness, infirmity, or imprisonment;

(D) that the party offering the deposition could not procure the witness's attendance by subpoena; or

(E) on motion and notice, that exceptional circumstances make it desirable — in the interest of justice and with due regard to the importance of live testimony in open court — to permit the deposition

UNITED STATES DISTRICT COURT
DISTRICT OF MASSACHUSETTS

IN RE NEW ENGLAND COMPOUNDING PHARMACY, INC. PRODUCTS LIABILITY LITIGATION _ _____	)	
THIS DOCUMENT RELATES TO: All Cases	)	MDL No. 2419 Dkt. No 1:13-md-2419 (RWZ)

SECOND AMENDED NOTICE OF 30(B)(6) DEPOSITION BY WRITTEN QUESTIONS

Defendants Box Hill Surgery Center, LLC, Ritu T. Bhambani, MD, and Ritu T. Bhambani, MD, LLC (Hereinafter "Box Hill"), pursuant to Fed. R. Civ. P. 31 and 30(b)(6), come now and give notice that the deposition of Cumberland Valley Surgery Center, as an organization, will be taken by written questions.

Pursuant to Fed. R. Civ. P. 30(b)(6) and 31(a)(4), Cumberland Valley Surgery Center shall designate a witness to testify regarding the written questions included with this notice, and any cross questions, redirect questions, or recross questions submitted in accordance with Fed. R. Civ. P. 31(a)(5).

The deponent will testify before a court reporter from Discovery Litigation Services at Cumberland Valley Surgery Center, 1110 Professional Court, #100, Hagerstown, Maryland 21740 **on February 25, 2016 at 11:00AM EST** [1]. The deposition will be recorded by video and stenographical means.

[1] Time amended

Respectfully submitted,

/s/ Gregory K. Kirby
Gregory K. Kirby
Pessin Katz Law, PA
901 Dulaney Valley Road
Suite 400
Towson, MD 21204
(410) 938-8800
gkirby@pklaw.com

Attorneys for Box Hill Surgery Center, LLC, Ritu T. Bhambani, MD, and Ritu T. Bhambani, MD, LLC

CERTIFICATE OF SERVICE

I, Gregory K. Kirby, hereby certify that:

1. A copy of the forgoing document, filed through the CM/ECF system will be accessible to those attorneys who are registered with the Court's electronic filing system, including the attorneys representing the Plaintiffs in suits against Box Hill

2. Notice of Electronic Filing (NEF) will be sent to those parties by operation of CM/ECF system

3. A copy of the document will be served by U.S. Mail to April Hitzelberger, Esquire, Waranch & Brown, LLC, 1301 York Road, Suite 300, Lutherville, Maryland 21093.

on February 22, 2016.

/s/ Gregory K. Kirby
Gregory K. Kirby

DIRECT EXAMINATION QUESTIONS

THE FOLLOWING **21 QUESTIONS** ARE SUBMITTED BY THE BOX HILL DEFENDANTS, AND ARE TO BE READ AND ANSWERED **FIRST**. THERE ARE NO ACCOMPANYING EXHIBITS

UNITED STATES DISTRICT COURT
DISTRICT OF MASSACHUSETTS

IN RE NEW ENGLAND COMPOUNDING PHARMACY, INC. PRODUCTS LIABILITY LITIGATION	MDL No. 2419 Dkt. No 1:13-md-2419 (RWZ)
THIS DOCUMENT RELATES TO: All Cases	

DEPOSITION BY WRITTEN QUESTIONS OF CUMBERLAND VALLEY SURGERY CENTER

Pursuant to Fed. R. Civ. P. 31, Box Hill Surgery Center, LLC, Ritu T. Bhambani, MD, and Ritu T. Bhambani, MD, LLC (Hereinafter "Box Hill") hereby submit the following questions to Cumberland Valley Surgery Center, to be answered by one or more individuals with knowledge of Cumberland Valley Center's medication purchasing practices (and, specifically, its purchases from New England Compounding Center ("NECC")), to be designated by Cumberland Valley Surgery Center in accordance with Fed. R. Civ. P. 30(b)(6).

Background

1. Please state your name.

2. Please provide your complete address and phone number with area code.

3. Do you work at Cumberland Valley Surgery Center? If so[1]:

   a. What is your current position?

   b. How long have you held that position?

   c. Please describe your job duties at Cumberland Valley Surgery Center.

[1] If not, please state your employer, position, and job duties.

4. Please provide a brief summary of your educational and employment background, leading up to your present position at Cumberland Valley Surgery Center.

5. Please provide a general description of your facility (*e.g.*, type of practice, number of physicians, *etc.*).

6. By virtue of your role at Cumberland Valley Surgery Center, are you familiar with Cumberland Valley Surgery Center's medication purchasing practices?

7. Please describe the basis for your familiarity with Cumberland Valley Surgery Center's medication purchasing practices (*e.g.*, is it from personal knowledge? have you spoken with persons at Cumberland Valley Surgery Center or reviewed documents?).

Purchases from NECC and actions prior to purchase

8. For the years 2010 through 2012, did Cumberland Valley Surgery Center purchase medications offered for sale by Medical Sales Management and/or New England Compounding Center and made by the New England Compounding Center (hereinafter "NECC")?

9. Please describe the timeframes that Cumberland Valley Surgery Center purchased medications from NECC and what medications were purchased.

10. Prior to purchasing medications from NECC, did a representative of Cumberland Valley Surgery Center perform an in-person inspection of NECC's compounding facility? If so, please (1) state when, (2) describe what was done and what was found, and (3) state whether, following the inspection, Cumberland Valley Surgery Center purchased medications from NECC.

11. Prior to purchasing medications from NECC, did Cumberland Valley Surgery Center conduct research into whether NECC had recalled any medications made by NECC? If so, please (1) describe the research conducted, (2) describe the results, and (3) state whether, following the drug recall research, Cumberland Valley Surgery Center purchased medications from NECC.

12. Prior to purchasing medications from NECC, did Cumberland Valley Surgery Center conduct research into whether NECC had ever been named as a defendant in a products liability lawsuit? If so, please (1) describe the research conducted, (2) describe the results, and (3) state whether, following the previous lawsuit research, Cumberland Valley Surgery Center purchased medications from NECC.

13. Prior to purchasing medications from NECC, did Cumberland Valley Surgery Center request information from the Massachusetts Board of Registration in Pharmacy (the "Board") about previous disciplinary actions taken by the Board against NECC? If so, please (1) describe what information was provided by the Massachusetts Board of

Registration in Pharmacy and (2) state whether, following the request, Cumberland Valley Surgery Center purchased medications from NECC.

14. Prior to purchasing medications from NECC, did Cumberland Valley Surgery Center submit a Freedom of Information Act request to the FDA for documentation of disciplinary actions and/or warnings issued to NECC by the FDA? If so, please (1) describe what information was provided by the FDA and (2) state whether, following the request, Cumberland Valley Surgery Center purchased medications from NECC.

15. Prior to purchasing medications from NECC, did Cumberland Valley Surgery Center search the FDA website for information about NECC? If so, please (1) describe what information was obtained from the FDA website and (2) state whether, following the request, Cumberland Valley Surgery Center purchased medications from NECC.

16. Prior to purchasing medications from NECC, did Cumberland Valley Surgery Center review transcripts from or summaries of any U.S. Congressional hearings on compounding pharmacies? If so, following the review, did Cumberland Valley Surgery Center purchase medications from NECC?

17. At the time of Cumberland Valley Surgery Center's purchases from NECC, did Cumberland Valley Surgery Center have a policy and/or procedure in place prohibiting purchases from compounding pharmacies?

18. Please describe any representations Medical Sales Management and/or NECC made to Cumberland Valley Surgery Center prior to Cumberland Valley Surgery Center purchasing medications from NECC.

19. In deciding to purchase medications from NECC, did Cumberland Valley Surgery Center take into consideration any representations from Medical Sales Management and/or NECC regarding its ability to provide a consistent supply of safe medications?

20. Prior to purchasing from NECC, did Cumberland Valley Surgery Center research compounding pharmacies in CDC literature, *USA Today*, FDA literature, or on YouTube? If so, please (1) describe the research and (2) state whether, following the research, Cumberland Valley Surgery Center purchased medications from NECC.

21. To the best of your knowledge, did any of Cumberland Valley Surgery Center's patients experience an injury as a result of Cumberland Valley Surgery Center's purchase, and use, of medications from NECC which were administered to Cumberland Valley Surgery Center's patients?

Respectfully submitted,

/s/ Gregory K. Kirby
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(410) 938-8800
gkirby@pklaw.com

Attorneys for Box Hill Surgery Center, LLC, Ritu T. Bhambani, MD, and Ritu T. Bhambani, MD, LLC

CERTIFICATE OF SERVICE

I, Gregory K. Kirby, hereby certify that:

1. A copy of the forgoing document, filed through the CM/ECF system will be accessible to those attorneys who are registered with the Court's electronic filing system, including the attorneys representing the Plaintiffs in suits against Box Hill

2. Notice of Electronic Filing (NEF) will be sent to those parties by operation of CM/ECF system

3. A copy of the document will be served by U.S. Mail and Hand Delivery to Cumberland Valley Surgery Center, 1110 Professional Court, Hagerstown, MD 21740

on October 12, 2015.

/s/ Gregory K. Kirby
Gregory K. Kirby

CROSS – EXAMINATION QUESTIONS

THE FOLLOWING **104 QUESTIONS AND ACCOMPANYING MATERIALS** ARE SUBMITTED BY THE PLAINTIFF STEERING COMMITTEE. THESE QUESTIONS ARE TO BE READ AND ANSWERED **SECOND** (ONCE ALL DIRECT EXAMINATION QUESTIONS HAVE BEEN ASKED AND ANSWERED).

RULE 31 CROSS-EXAM QUESTIONS FOR RULE 31 DEPOSITION OF CUMBERLAND VALLEY SURGERY CENTER ("CVSC")

1. When did you receive the written deposition questions that were served upon you?

2. As this is a deposition upon written questions, you have been provided in advance with every question that will be asked of you today, correct?

3. Is it correct that you have had an opportunity to consult with an attorney in drafting the answers to those written questions?

4. And an attorney assisted you in preparing answers to the written questions, correct?

5. What is the attorney's name?

6. And you understand that one of the limitations of a deposition upon written questions is that we do not know what your answers will be when we drafted the questions that we submitted?

7. Did you or your attorney have any conversations or other communications with any of the attorneys representing Box Hill, Premier or Saint Thomas Outpatient Neurosurgical Center?

    a) (If yes) Please state the date and substance of each such conversation or communication.

8. Do you have with you any written answers or written notes to answer the written questions which were served upon you?

    a) (If yes) Can you produce those answers or notes to me so that I may mark it as an exhibit?

    (Mark as Exhibit ___)

9. What documents did you review in preparing your answers or notes to the written questions served upon you?

10. Did anyone assist you in preparing these written answers or notes?

    a) (If yes)

        1) Who assisted you?

2) What is his or her position?

11. Is it correct that Cumberland Valley Surgery Center, which I will refer to as "CVSC," ordered a number of different products from NECC between 2010 and 2012, including preservative free omnipaque, preservative free betamethasone and preservative free bupivacaine?

12. Is it correct that CVSC never purchased any preservative-free methylprednisolone acetate, which I will refer to as "MPA," from NECC?

13. Did you work at CVSC prior to the time when CVSC began ordering drugs from NECC?

a) (If yes) Were you personally involved in the decision to purchase drugs from NECC?

b) (If no) Who at CVSC was involved in the decision to purchase drugs from NECC?

14. Please provide the current work and home address of each person who was involved in the decision to purchase drugs from NECC.

15. Let me show you an article entitled "GMP and Compounding Pharmacies" by Scott Sutton, which I have marked as Exhibit ___. Please turn to page 55. Looking at the last line of Table 2, between January 1, 2010 and September 25, 2012, was CVSC aware that, in 1990, "[f]our patients died of an *Enterobacter* infection from a filter-sterilized cardioplegia solution (a parenteral with high potential for bacteremia) compounded in a Nebraska hospital" and that "five bottles of the solution tested were nonsterile, several subsequent bottles tested were sterile, and another 93 bottles were dispensed without being tested"?

16. Turning to page 56 of the Sutton article, Ex. ___, under the heading "Compounding Pharmacies and Contamination Issues," between January 1, 2010 and September 25, 2012, was CVSC aware that "[b]y the mid-1990s FDA was investigating a number of pharmacies that were operating as manufacturing facilities in response to a number of contamination events"?

17. Prior to September 25, 2012, did CVSC do any investigation of NECC to determine if it was operating as a manufacturing facility?

a) (If yes) Please describe that investigation.

18. Prior to September 25, 2012, what, if any, investigation did CVSC conduct to determine the volume of drugs that NECC was compounding?

19. Let's turn back to the Sutton article, Ex. ___, page 55, Table 2. Between January 1, 2010 and September 25, 2012, was CVSC aware that, in 1998, "11 children became septic in California and 10 tested positive for *Enterobacter cloacae* bloodstream infections associated with contaminated prefilled saline syringes from CAPS, Braun-McGaw of Detroit, MI"?

20. Looking again at Table 2 on page 55 of the Sutton Article, between January 1, 2010 and September 25, 2012, was CVSC aware that, in 1999, a "[s]urvey of compounded Alprostadil formulations from a variety of sources showed contamination in 18% of samples tested"?

21. And looking again at Table 2 on page 55 of the Sutton Article, between January 1, 2010 and September 25, 2012, was CVSC aware that, in 2001, "13 patients (3 facilities) came down with bacterial meningitis after receiving contaminated compounded bethamethasone injections prepared by Doc's Pharmacy in California"?

22. Please turn back to page 55, Table 2, of the Sutton article. Between January 1, 2010 and September 25, 2012, was CVSC aware that in 2001 "4 children contracted *Enterobacter cloacae* infections from IV ranitidine compounded in a hospital pharmacy"?

23. Looking at Table 2 on this same page of the Sutton Article, between January 1, 2010 and September 25, 2012, was CVSC aware that, in 2001, "Med-Mart Pulmonary Services of California was forced to recall five lots of Albuterol (an inhalant) due to contamination by *Serratia liquefaciens*"?

24. Looking at Table 2 on this same page of the Sutton Article, between January 1, 2010 and September 25, 2012, was CVSC aware that, in 2002, "MMWR reported on *Exophiala* (*Wangiella*) *dermatitidis* infections from contaminated injectable methyl-Prednisolone prepared by a compounding pharmacy" and that "one patient died"?

25. Looking at Table 2 on this same page of the Sutton Article, between January 1, 2010 and September 25, 2012, was CVSC aware that, in 2003, "[b]acteria contamination with *Burkholderia cepacia* was found in at least 2 batches of a compounded inhalant solution used by 19,000 patients nationwide with chronic lung diseases"?

26. Looking at Table 2 on this same page of the Sutton Article, between January 1, 2010 and September 25, 2012, was CVSC aware that, in 2004, "36 patients developed

Pseudomonas bloodstream infections after receiving heparin/saline flushes from multiple lots of preloaded syringes by Pinnacle Medical Supply of Rowlett, TX"?

27. Looking at Table 2 on this same page of the Sutton Article, between January 1, 2010 and September 25, 2012, was CVSC aware that, in 2004, "2 patients reported with life-threatening sepsis caused by *Burkolderia cepacia* from contaminated intravenous flush solutions that had been shipped across state lines"?

28. Looking at Table 2 on this same page of the Sutton Article, between January 1, 2010 and September 25, 2012, was CVSC aware that, in 2004, "16 patients were reported with Hepatitis C virus infections from a contaminated radiopharmaceutical used in myocardial perfusion studies"?

29. Looking at Table 2 on this same page of the Sutton Article, between January 1, 2010 and September 25, 2012, was CVSC aware that, in 2005, "[u]p to 25 patients in New Jersey and California contracted *Serratia marcescens* infections due to contaminated magnesium sulfate prepared by Pharmedium, a compounding pharmacy located in Lake Forest, IL"?

30. Looking at Table 2 on this same page of the Sutton Article, between January 1, 2010 and September 25, 2012, was CVSC aware that, in 2005, "6 cases of postsurgical endophthalmitis were reported due [to] a compounded trypan blue ophthalmic injection contaminated with *Pseudomonas aeruginosa* and *Burkholderia cepacia*" and "recalled by the compounding pharmacy Custom-RZ of Richfield, MN"?

31. Looking at Table 2 on this same page of the Sutton Article, between January 1, 2010 and September 25, 2012, was CVSC aware that, in 2005, "10 patients died in Virginia after exposure to cardioplegia solution from 2 lots contaminated with gram-negative rods" that were "made by Central Admixture Pharmacy Services, Inc. (CAPS), a subsidiary of B. Braun Medical located in Maryland"?

32. CVSC is located in Haggerstown, Maryland, is that correct?

33. CVSC was operating in 2005 when this contaminated product was distributed from a compounding pharmacy in Maryland, is that correct?

34. And that 2005 outbreak resulted in 10 deaths in CVSC's neighboring state, Virginia, is that correct?

35. Let me show you this January 10, 2006 Consent Order between the Maryland CAPS compounding pharmacy and the Maryland State Board of Pharmacy that was publically available on the Maryland Department of Health's website, which I will mark as Exhibit ___.

36. Between January 1, 2010 and September 25, 2012, was CVSC aware of this consent order involving Maryland CAPS compounding pharmacy?

37. Please turn to page 5 of the consent order, Ex. __, and read out loud paragraph 13 and subsections a-p of paragraph 13, which continues on pages 6 and 7.

38. And please read out loud paragraph 14 of the consent order, Ex. __, on page 7.

39. Let me show you this March 15, 2006 Warning Letter from the FDA issued to the Maryland CAPS compounding pharmacy that was publically available on the FDA's website, which I will mark as Ex. __.

40. Please read out loud the last sentence beginning on the bottom of page 2 and the first full sentence on the top of page 3 of the March 15, 2006 Warning Letter issued to the Maryland CAPS compounding pharmacy.

41. Let me show you what has been previously marked as Exhibit 318, a USA Today article published on August 7, 2006 and entitled "Deaths spur debate about drugs made in pharmacies." Can you please read the fourth paragraph on page 1 (beginning with the words "The hospital later determined…")?

42. Between January 1, 2010 and September 25, 2012, was CVSC aware that compounding pharmacies were compounding high risk sterile preparations "under less restrictive rules than those that drug companies follow"?

43. Can you please read out loud the second sentence of the sixth paragraph on page 1 (beginning with the words "The frequency and thoroughness…")?

44. Between January 1, 2010 and September 25, 2012, was CVSC aware that the frequency and thoroughness of state inspections of pharmacies vary widely and the FDA's oversight is sometimes hampered by questions over whether it has jurisdiction over what is generally a state matter"?

a) (If yes) Did CVSC consider the lack of FDA oversight over compounding pharmacies and the lack of state inspections of compounding pharmacies when it decided to purchase drugs from NECC?

45. Please read out loud the seventh full paragraph of the 2006 USA Article, Ex. 318 (beginning with the words "scrutiny of the pharmacy that served…").

46. Turning back to the Sutton Article, Ex. __, at page 55, Table 2, between January 1, 2010 and September 25, 2012, was CVSC aware that, in 2005, "*Pseudomonas putida* septicemia was reported in a special care nursery due to contaminated flush solutions prepared in a hospital pharmacy" and that "36 cases of *Pseudomonas fluorescens* bloodstream infections were associated with a heparin/saline flush"?

47. Looking at Table 2 on this same page of the Sutton Article, between January 1, 2010 and September 25, 2012, was CVSC aware that, in 2007, "[e]ight cases of *Sphingomonas paucimobilis* bloodstream infections were associated with contaminated intravenous fentanyl"?

48. Looking at Table 2 on this same page of the Sutton Article, prior to September 25, 2012, was CVSC aware that, in 2011 "9 patients died of the 19 total taken ill in Alabama when parenteral nutrition solutions that were administered were contaminated with *Serratia marcescens* during compounding using non-sterile components to prepare amino acids"?

49. Looking at Table 2 on this same page of the Sutton Article, prior to September 25, 2012, was CVSC aware that in 2011 "16 people in Florida and Tennessee [became] infected when a compounding pharmacy in Hollywood, CA repackaged Avastin for off-label eye injections…[which] resulted in blindness for some"?

50. Looking at Table 2 on this same page of the Sutton Article, prior to September 25, 2012, was CVSC aware that in 2012, "33 people across 7 states contracted fungal endophthalmitis leading to the recall of 6 months' worth of all compounded batches from Franck's Pharmacy"?

51. Let me show you what has previously been marked as Exhibit 317 (FDA Consumer Health Info.) Between January 1, 2010 and September 25, 2012, was CVSC aware that, in 2007, the FDA published a report entitled "The Special Risks of Pharmacy Compounding," which reported that the Agency had reports of more than 200 adverse reports at that time, involving 71 compounded products since 1990?

a) (If yes) Did CVSC consider that the number of reported adverse events involving compounded drugs could be much lower than the number of actual adverse effects?

52. Turning back to p.56 of the Sutton Article, between January 1, 2010 and September 25, 2012, was CVSC aware that "adverse event reporting is rare for pharmacy products…because, in contrast to products that are subject to approved drug applications, there are no adverse event reporting requirements for drugs made by pharmacies"?

53. Let me show you an article, entitled "Pharmacy Compounding Primer for Physicians," which was written by Sarah Sellers and which I will mark as Ex. ___. Please turn to the paragraph that begins on the bottom of the third page (starting with the words "In a 2004 published analysis…"). Between January 1, 2010 and September 25, 2012, was CVSC aware of a 2004 published analysis sponsored by STD Pharmaceuticals which found that all samples of 3% sodium tetradecyl sulfate solution purchased from three compounding pharmacies failed content testing and that significant concentrations of the contaminant carbitol were found to be present in the samples from all three compounding pharmacies?

54. Turning to the second paragraph on page 4 of the Sellers article (beginning with the words "Mahaguna et al. reported…"), between January 1, 2010 and September 25, 2012, was CVSC aware of a published analysis of compounded progesterone suppositories from ten randomly selected pharmacies, which found that 9 out of 10 pharmacies provided suppositories that fell outside potency limits for approved products and one pharmacy provided suppositories that tested positive for *Comanomal acidovorans* bacteremia?

55. Let me show you an article by G.J. Whelan, entitled "Subpotency of a Compounded Budesonide for a Nebulization Product in a Patient with Poorly Controlled Asthma," that was published in the Journal of Allergy and Clinical Immunology in 2006, which I will mark as Ex. ___. Between January 1, 2010 and September 25, 2012, was CVSC aware of a 2006 published report of a probable treatment failure in a poorly controlled asthma patient where an analysis of the inhalation drug only contained an average of 36.8% of the active ingredient in which the authors noted that "use of compounded products are generally discouraged due to concerns of stability and sterility"?

56. Going back to the fifth full paragraph on page 3 of the Sellers article, Ex. ___ (starting with the words "In 2006, the FDA conducted…"), between January 1, 2010 and September 25, 2012, was CVSC aware that, in 2006, the FDA conducted a limited survey of compounded drugs and of 36 samples tested, 12 failed at least one quality test, for a failure rate of 33%?

57. Looking at the second full paragraph on page 4 of the Sellers article, Ex. ___ (starting with the words "In a similar analysis…"), between May 1, 2012 and September 25, 2012, was CVSC aware of a May 2012 published report where 16 out of 30 samples of hydroxyprogesterone injections purchased from compounding pharmacies exceeded impurity limits for the comparable FDA-approved product?

58. Let me show you what I have marked as Exhibit ___. This is a 2010 publication entitled USP 797 Gap Analysis Tool. Prior to September 25, 2012, was CVSC aware of what USP 797 was?

59. Prior to September 25, 2012, was CVSC aware of what a Gap Analysis Tool was?

60. Please turn to page 3 of the 2010 USP 797 Gap Analysis Tool. Can you please read out loud the first sentence under the Introduction header (beginning with the words "Over the years…")?

61. Prior to September 25, 2012, was CVSC aware that many healthcare providers refused to order from compounding pharmacies due to safety concerns?

62. Let me show you what has been previously marked as Exhibit 305, a 2003 FDA Enforcement Report that was posted on its website. Looking at pages 3 and 4 of this exhibit, between January 1, 2010 and September 25, 2012, was CVSC aware that NECC had recalled several lots of Betamethasone in February 2003 and that it had recalled preservative-free methylprednisolone during the summer of 2002?

63. Let me show you what has been previously marked as Exhibit 306, a 2006 warning letter from the FDA to NECC. Between January 1, 2010 and September 25, 2012, was CVSC aware that the FDA had issued a Warning Letter to NECC on December 4, 2006, in which it raised safety concerns regarding NECC's compounding practices?

64. Could you please read out loud the sixth full paragraph on page 3 of Exhibit 306, the 2006 FDA warning letter to NECC (beginning with the words "The agency has an established policy…")?

65. Between January 1, 2010 and September 25, 2012, was CVSC aware that, in 2010, the American Society of Health System Pharmacists ("ASHP") had published a set of guidelines for health systems on outsourcing sterile compounding services?

66. Let me show you what has been previously marked as Exhibit 751. These are the 2010 ASHP Guidelines on Outsourcing Sterile Compounding Services. Please turn to the first page (page 372). Under the section entitled "Purpose," can you please read out loud the first two sentences (beginning with the words "Health care organizations considering…")?

67. Can you turn to page 374 of this same exhibit and read out loud the first two sentences of the second paragraph under the section entitled "Outsourcing Process" (beginning with the words "Some organizations simply…")?

68. And on the same page of this exhibit, under the subsection entitled "Contents of Proposals" can you please read out loud the first sentence (beginning with the words "RFPs should require…")?

69. In the same subsection, can you please read out loud the sixth bullet point (beginning with the words "Evidence of the following documentation…") and the second sub-bullet point under that (beginning with the words "Current accreditation…")?

70. What accreditation or certification certificates did NECC provide to CVSC?

71. Did CVSC ever ask either NECC or the Pharmacy Compounding Accreditation Board ("PCAB") whether NECC was accredited by the PCAB?

72. Before September 25, 2012 was CVSC aware of the PCAB?

73. Please turn back to page 374 of Exhibit 751 and to the same subsection entitled "Contents of Proposals." Can you please read out loud the next sub-bullet point (beginning with the words "Licensure documents…")?

74. Prior to September 25, 2012, did CVSC ever ask NECC whether it was registered with the FDA as a drug establishment?

    a) (If yes) What was NECC's response?

    b) (If no) Prior to September 25, 2012, was CVSC aware of the difference between a drug manufacturer and a compounding pharmacy?

75. Prior to September 25, 2012, was CVSC aware that drug manufacturers were required to be registered with the FDA and had to follow current Good Manufacturing Practices ("cGMPs")?

76. Prior to September 25, 2012, was CVSC aware of what cGMPs were?

77. Please turn back to Exhibit 751 and turn to page 375. Looking at the bullet points at the top left section of the page concerning contents of proposals from compounding pharmacies, please read out loud the seventh bullet point (beginning with the words "Examples of batch reports…").

78. Prior to September 25, 2012, did CVSC request examples of batch reports for the drugs it obtained from NECC?

a) (If yes) 1) Which Logged Formula Worksheets was CVSC supplied with by NECC? 2) Did the Logged Formula Worksheets indicate if the products were sterilized?

b) (If no) Did CVSC make any inquiry concerning NECC's compounding and sterilization procedures?

79. Please return to Exhibit 751. Do you see on page 375, on the left hand side, where the guidelines state that a compounding pharmacy should provide "[a] history of the results of all accreditation or regulatory surveys conducted of the compounding pharmacy's sites, including copies of significant regulatory actions"?

80. Prior to September 25, 2012, did CVSC ever request NECC to provide copies of significant regulatory actions taken against it?

81. Prior to September 25, 2012, was CVSC aware that NECC was registered as a pharmacy with the Massachusetts Board of Registration in Pharmacy ("BoRP")?

82. Prior to September 25, 2012 did CVSC know that the BoRP had taken a number of regulatory actions against NECC and that these actions were a matter of public record?

83. Turning back to page 375 of Exhibit 751, in the section concerning information that the compounding pharmacy should provide in a RFP, can you please read out loud the third bullet point from the bottom on the left side (beginning with the words "Examples of reports…")?

84. Prior to September 25, 2012, did CVSC request NECC to provide examples of the reports it would provide on the drugs it was compounding for CVSC?

85. Prior to September 25, 2012, was CVSC aware that it could order the sterility test results on each batch lot of the drugs that CVSC was ordering and that NECC would send the sterility test results with each order?

86. Did CVSC ensure that each of the lots of the drugs that it ordered from NECC between January 1, 2010 and September 25, 2012 had undergone a sterility test for 14 days before administering those drugs to CVSC's patients?

87. Prior to September 25, 2012, did CVSC receive sterility test reports with its drug orders from NECC?

a) (If yes) 1) Did CVSC review and understand the sterility test results? 2) Did the sterility test results indicate how many sample units of the drugs had been tested for sterility?

88. Please turn back to page 375 of Exhibit 751. Looking on the right side of the page, can you please read out loud the first bullet point under the phrase "Additional information to obtain from the prospective compounding pharmacy but not necessarily contained in the proposal may include"?

89. Prior to September 25, 2012, did CVSC request NECC to provide any information concerning prior product liability lawsuits against it?

a) (If yes) 1) What information did NECC provide? 2) When did NECC provide such information?

b) (If no) Prior to September 25, 2012, was CVSC aware that NECC had been sued in a 2004 product liability lawsuit involving one of its compounded steroids and that NECC had settled that case in 2007?

90. Turning back to Exhibit 751, page 375, can you please read out loud the second bullet point on the right hand side under the bullet point concerning product liability lawsuits (beginning with the words "A description of the compounding pharmacy's…")?

91. Prior to September 25, 2012, had CVSC ever inquired of NECC as to whether NECC had recalled any of its compounded products?

92. Turn back to Exhibit 751, p. 375. On the right hand side, can you please read out loud the two sentences under the section "Visits to Compounding Pharmacies and Their Clients" (beginning with the words "Compounding pharmacies should allow…")?

93. Prior to September 25, 2012, did NECC allow CVSC to visit its compounding facility?

94. Let me show you what has previously been marked as Exhibit 526. Do you recognize this as a NECC brochure that was distributed to healthcare providers?

95. Do you see on the first page, section D.c., that NECC informed healthcare providers that "[s]amples from final product batch lots are sent to an independent FDA registered analytical lab for sterility, endotoxin (pyrogenicity) and potency testing"?

96. Prior to September 25, 2012, what was CVSC's understanding of the term "final product batch lots"?

97. Did CVSC ever inquire of NECC as to what "final product batch lots" were?

98. Please turn to the second page of Ex. 526, section G, and read that out loud.

99. Between January 1, 2010 and September 25, 2012, was CVSC aware that a patient-specific prescription was required in order for a drug to be dispensed by NECC?

100. Between January 1, 2010 and September 25, 2012, was CVSC part of a larger health system?

a) (If yes) Please explain CVSC's affiliation with the larger health system.

101. Between January 1, 2010 and September 25, 2012, did CVSC or its health system have any policies and/or procedures in place regarding the ordering of high risk compounded drugs for its patients?

a) (If yes) Please describe those policies and/or procedures.

102. For each order of a drug CVSC purchased from NECC between January 1, 2010 and September 25, 2012, please state whether it was on CVSC's drug formulary at the time it was ordered from NECC.

103. Between January 1, 2010 and September 25, 2012, was there anyone at CVSC who had expertise in microbiology?

a) (If yes) Please identify those individuals and state whether each was involved in the decision to purchase drugs from NECC.

104. For each of the drugs that CVSC ordered from NECC between January 1, 2010 and September 25, 2012, please state the following:

Did CVSC purchase that drug from any other source between January 1, 2006 and December 31, 2015?

(If yes) Please state a) the price paid for each such purchase; b) the entity(s) each such drug was ordered from; c) whether each such entity was registered with the FDA at the time of each such order; and d) please describe any investigation CVSC conducted of each such entity.

GMP and Compounding Pharmacies

[redacted]

It seems self-evident today, but worth remembering, that the pharmaceutical industry exists on a foundation of trust. Patients or even doctors have no way to actually determine the strength, purity and quality of the medicines prescribed and taken. Everyone trusts that the label is accurate and the medicines are pure. This was not always the case and efforts to safeguard our medicine supply led directly to USP, FDA and the GMPs.

Recently we have been reminded of the critical nature microbial Quality control plays in safe medications as contaminated medicine shipped nationally from a compounding pharmacy has sickened hundreds. The New England Compounding Center (NECC) of Framingham, MA was responsible for the manufacture of preservative-free methylprednisolone acetate. This was an aseptically produced parenteral, delivered intrathecally (directly to the spinal column, bypassing most of the body's defense mechanisms).

It is difficult to envision a more hazardous situation and the results have been disastrous. Three lots of this product have exposed over 20,000 individuals to risk of fungal meningitis, and by latest count (April 15, 2013 - http://www.cdc.gov/hai/outbreaks/meningitis-map.html) have resulted in infections in 733 patients and 53 deaths associated with these intrinsically contaminated medicines.

In response to this situation, FDA has embarked on an aggressive inspection schedule that resulted in multiple 483 findings in the beginning of 2013 (summarized in Table 1). Review of these 483 observations shows several common findings among the compounding pharmacies that received 483 observations during this time:

- Lack of procedures to prevent microbial contamination
- Problems with the Environmental Monitoring program
- Problems with batch release
- Lack of validation of the sterilization method
- Inadequate control/cleaning/qualification of critical equipment used in manufacture
- Issues with personnel gowning

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- Expiry dating of manufactured medicines not supported by a stability study
- Issues with laboratory procedures or control of contract lab
- Issues with investigations
- Control of incoming raw materials and components

These (and others listed in Table 1) are basic GMP requirements, and described in 21 CFR 211 as well as many also being discussed in USP <797> *Pharmaceutical Compounding – Sterile Preparations*. For the moment, we will leave USP chapter <797> for discussion later in the article and focus for now on GMP. At a time when we are looking at compounding pharmacies that are functioning as pharmaceutical manufacturers, we need to look back at where pharma was and how we got here, and the genesis and development of the GMP as described in 21 CFR 210/211.

FDA & GMP

A recent review [1] describes the development of FDA oversight of pharma. Originally the Drug Laboratory in the Bureau of Chemistry (US Department of Agriculture), it was created in 1906 through the Pure Food and Drugs Act. As an agency, however, it was toothless to affect the streams of fraudulent claims and questionable ingredients,

[illegible]

	SOPs to Prevent Microbial Contamination Non-existent or Not Followed	Inadequate/ Improper EM	Stability Program	Inadequate Gowning	Batch Release	Validation of Sterilization	Lab Procedures: Testing/ Contract Lab Control
Anazaohealth	1	4	8	5	3	2	11
Avella of Deer Valley	3	2		1	6	4	
Balanced Solutions Compounding	3	4	9	6	1, 7	5	
CAPS (Central Admixture Pharmacy Services) (Chicago)		2	7	3	1	6	
CAPS (Homewood, AL)	6	6	9, 12	4	1, 2		11
CAPS (Kansas City)	2	3		2	4		1
CAPS (Livonia)	3, 5				6		
College Pharmacy, Inc		1	5		2, 6	4	2
Compounding Shop, The	1	2	11	9	4, 10	5	4
Drugs Are Us		1	3	2			
Foundation Care, LLC	1			2	4		3
Home Intensive Care Pharmacy	1	5	6	2			
IV Solutions of Lubbock	5	4	7	1			
Lee Pharmacy	3	1	5			2	
Lowlyn Pharmacies, Inc	1	3	11	5	9, 10	2	
Medaus	3	4	10	2		1	8, 9
Medi-Fare Drug & Home Care Center		6	7, 12		1, 3	2, 4	8
NECC		3, 4					
Nora Apothecary and Alternative Therapies, Inc	3	4	5		2		1, 2
Oakdell Pharmacy	1	5	6	2		7	
Olympia Pharmacy	2	4	9	6		1	11, 12
Pentec Health	8		6	2		1	5
PharMEDium Services (Cleveland)	5		10, 11		3, 9	2	2, 3, 9
PharMEDium Services (Edison, NJ)	5		4	1	3		2
PharMEDium Services (Memphis, TN)	3		6, 12		5, 7	6	4, 5
PharMEDium Services (Sugarland, TX)	3	8	6, 7, 9	2	4, 5		4
Portage Pharmacy	1	3	10, 11	4	2, 6, 7, 8		9, 12
Specialty Compounding	1	3	5	2	7	4	6
Triangle Compounding	4	3				2	
University Pharmacy	4	5	6		2	3	
Wedgewood Village Pharmacy				1	3, 10	4	3, 9

	Control of Equipment	Inadequate Cleaning/ Disinfection	Inadequate Facility	Control of Pyrogenic Contamination	Investigations	Inadequate raw material control	Separation of Clean and Dirty Operations/ Storage of Materials
Anazaohealth	12	6	.	9, 11	.	10	.
Avella of Deer Valley	5	.	.	.	7	.	.
Balanced Solutions Compounding	2	.	.	7	.	.	8
CAPS (Central Admixture Pharmacy Services) (Chicago)	.	.	5	.	.	.	4
CAPS (Homewood, AL)	8	7	5	.	3, 10	.	.
CAPS (Kansas City)	6	.	.	.	5	.	.
CAPS (Livonia)	.	.	1, 4	.	.	7	.
College Pharmacy, Inc	.	.	1	.	.	3	1
Compounding Shop, The	3, 12	7	6	8	.	.	.
Drugs Are Us	.	.	.	.	.	.	.
Foundation Care, LLC	6	7	.	4	.	5	.
Home Intensive Care Pharmacy	.	4	.	.	.	.	3
IV Solutions of Lubbock	3	.	2, 6	.	.	.	.
Lee Pharmacy	.	.	.	.	.	6	.
Lowlyn Pharmacies, Inc	12	6, 12	.	9	.	.	7
Medaus	.	12	5	.	.	6, 11	.
Medi-Fare Drug & Home Care Center	.	.	.	4	10, 11	1	.
NECC	5	.	5	.	3	2	.
Nora Apothecary and Alternative Therapies, Inc	.	6	.	1	.	.	.
Oakdell Pharmacy	.	4	.	.	.	.	3
Olympia Pharmacy	.	7	5	10, 11	.	.	3
Pentac Health	4	.	3	.	7	9	.
PharMEDium Services (Cleveland)	6, 7	.	1, 8	2	.	.	.
PharMEDium Services (Edison, NJ)	.	.	.	2	7	.	.
PharMEDium Services (Memphis, TN)	.	.	2	5	10	.	11
PharMEDium Services (Sugarland, TX)	1	1	.	.	.	.	.
Portage Pharmacy	.	.	.	8	.	.	.
Specialty Compounding	.	8	.	.	.	.	.
Triangle Compounding	5	.	.	.	1	.	.
University Pharmacy	5	1, 5	.	2	.	.	.
Wedgewood Village Pharmacy	.	.	.	.	7	5, 6	.

(opium and morphine were very popular for their all-around curative properties), until the 1938 Food, Drug, and Cosmetic Act. This increased authority was direct response to the perceived need for a federal level control on medicines sparked by the production of a sulfonamide elixir using diethyl glycol in their oral product. This situation led to the death of 107 people. FDA was soon faced with another situation in 1941 with the release of sulfathiazole tablets containing phenobarbital as a contaminant. This incident led to the death or injury of over 300 people and served as the impetus for a drastic revision of manufacturing and quality control practices [2, 3]. The further expansion of FDA authority and GMP followed in a series of steps, all reactionary in response to a threat to the public health from manufacturers failing the public trust.

This failure was not always (or even usually) traceable to malfeasance. In fact, most of the cases seemed, in hindsight, to be due to ignorance on the part of the manufacturer as to the safety of his products (hence the requirement to document safety) or in

	QAU Not Effective/ Production SOPs not followed/ effective	SOP/ Control of Production	Safeguard Against Penicillin/ Cephalosporin Cross Contamination	Records not Available	Container Preparation	Change Control	Obvious Product Contamination	Personnel not Trained
Anazaohealth	7				9			
Avella of Deer Valley								
Balanced Solutions Compounding								
CAPS (Central Admixture Pharmacy Services) (Chicago)								
CAPS (Homewood, AL)								
CAPS (Kansas City)								
CAPS (Livonia)			2					
College Pharmacy, Inc								
Compounding Shop, The								
Drugs Are Us								
Foundation Care, LLC								
Home Intensive Care Pharmacy								
IV Solutions of Lubbock								
Lee Pharmacy	7	4						
Lowlyn Pharmacies, Inc				8				4
Medaus		7						
Medi-Fare Drug & Home Care Center	9	12		1, 5				
NECC							1	
Nora Apothecary and Alternative Therapies, Inc								
Oakdell Pharmacy								
Olympia Pharmacy								
Pentac Health								
PharMEDium Services (Cleveland)	13				12			
PharMEDium Services (Edison, NJ)					6			
PharMEDium Services (Memphis, TN)	1				9			
PharMEDium Services (Sugarland, TX)								
Portage Pharmacy	13		5	14				
Specialty Compounding								
Triangle Compounding		6						
University Pharmacy								
Wedgewood Village Pharmacy	1	5	8			11		

*These issues were identified during inspections posted early in 2013 (and New England Compounding Center) at the URL listed below.
NECC - http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORA/ORAElectronicReadingRoom/UCM325980.pdf
483s (checked April 15, 2013) http://www.fda.gov/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORA/ORAElectronicReadingRoom/ucm340853.htm
† These numbers reflect the observation number of the particular 483. Assignation of a particular 483 observation to a particular issue was performed solely by the author – some variations in interpretation are possible in these determinations. The compounding pharmacies are listed in alphabetical order while the issues are listed in frequency of citation. The numbers in the tables reflect the 483 observation number that prompted this notation (included to facilitate review against the particular 483). Please note there is a questionable correlation between the number of 483 observations and the severity of the situation at a particular location, although it may be indicative.

the manufacturing process. A frequently cited example of this is the Cutter incident involving the polio vaccine [4]. The inactivation methodology for the polio virus was not well characterized before the process was approved for use by several manufacturers. One of these (Cutter) made small changes to the process that resulted in incomplete inactivation of the virus in the vaccine. At the height

2012	• 33 people across 7 states contracted fungal endophthalmitis leading to the recall of 6 months' worth of all compounded batches from Franck's Pharmacy. This pharmacy also produces veterinary products (40% of 2005 sales). http://news.vin.com/VINNews.aspx?articleId=22724
	• Otc-Ease ear lubricant (a non-sterile product) was recalled due to potentially pathogenic microbial contamination. http://outbreaknews.com/2012/07/14/otc-ease%C2%AE-ear-lubricant-recalled-due-microbial-contamination/
	• As of February 4, 2014 687 patients contracted fungal meningitis after receiving methyl-Prednisolone acetate injection prepared by NECC (the current crisis related to compounding pharmacies) http://www.cdc.gov/hai/outbreaks/meningitis-map.html (numbers updated regularly)
2011	• 9 patients died of the 191total taken ill in Alabama when parenteral nutrition solutions that were administered were contaminated with *Serratia marcescens* during compounding using non-sterile components to prepare amino acids. The compounding pharmacy, Meds IV, was found to have the same strain of S. marcescens in the tap water faucet and the compounding equipment. http://www.npr.org/blogs/health/2011/03/30/134984222/nine-dead-in-ala-after-iv-treatment
	• 16 people in Florida and Tennessee infected when a compounding pharmacy in Hollywood, CA repackaged Avastin for off-label eye injections. Contaminated intra-ocular injections for age-related macular degeneration resulted in blindness for some. http://www.nytimes.com/2011/08/21/health/31drug.html?_r=3&
2007	• Eight cases of *Sphingomonas paucimobilis* bloodstream infections were associated with contaminated intravenous fentanyl. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2660711/
2005	• Up to 25 patients in New Jersey and California contracted *Serratia marcescens* infections due to contaminated magnesium sulfate prepared by Pharmedium, a compounding pharmacy located in Lake Forest, IL. http://www.ncbi.nlm.nih.gov/pubmed/17682984
	• 6 cases of postsurgical endophthalmitis were reported due a compounded trypan blue ophthalmic injection contaminated with *Pseudomonas aeruginosa* and *Burkholderia cepacia*. This was recalled by the compounding pharmacy Custom-RX of Richfield, MN. http://cid.oxfordjournals.org/content/48/11/1580.long
	• 10 patients died in Virginia after exposure to cardioplegia solution from 2 lots contaminated with gram-negative rods. This product was made by Central Admixture Pharmacy Services, Inc. (CAPS), a subsidiary of B. Braun Medical located in Maryland (also see 1998 incident below). http://richmond.legalexaminer.com/defective-and-dangerous-products/cluster-of-heart-surgery-patient-deaths-linked-to-contaminated-cardioplegia-made-by-a-compounding-pharmacy.aspx?googleid=211240
	• *Pseudomonas putida* septicemia was reported in a special care nursery due to contaminated flush solutions prepared in a hospital pharmacy. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1248510/
	• 36 cases of *Pseudomonas fluorescens* bloodstream infections were associated with a heparin/saline flush. From the MMWR Report "To produce its heparin/saline flush, IV Flush ordered heparin powder and sent it to a compounding pharmacy, where a concentrated heparin solution was made. This concentrated solution was then returned to IV Flush, where it was added to bags of saline solution, from which the syringes were filled." IV Flush was located in Rowlett, Texas while the affected patients were in four states across the country. A later research paper identified potentially 80 cases. http://www.ncbi.nlm.nih.gov/pubmed/16960550 http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5411a1.htm http://cid.oxfordjournals.org/content/47/11/1372.full
2004	• 36 patients developed *Pseudomonas* bloodstream infections after receiving heparin/saline flushes from multiple lots of preloaded syringes by Pinnacle Medical Supply of Rowlett, TX. These infections occurred in Missouri, New York, Texas, and Michigan. http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5411a1.htm
	• 2 patients reported with life-threatening sepsis caused by *Burkholderia cepacia* from contaminated intravenous flush solutions that had been shipped across state lines. http://pediatrics.aappublications.org/content/116/1/e212.long
	• 16 patients were reported with Hepatitis C virus infections from a contaminated radiopharmaceutical used in myocardial perfusion studies. http://www.ncbi.nlm.nih.gov/pubmed/17062864
2003	• Bacteria contamination with *Burkholderia cepacia* was found in at least 2 batches of a compounded inhalant solution used by 19,000 patients nationwide with chronic lung diseases. Med 4 Home (Kansas City, MO) did only a partial recall of the batches, which totaled more than 1-million doses. http://www.sptimes.com/2003/04/18/news_pf/Business/Lincare_pharmacy_runs.shtml
2002	• MMWR reported on *Exophiala (Wangiella) dermatitidis* infections from contaminated injectable methyl-Prednisolone prepared by a compounding pharmacy; one patient died. NOTE that this report describes fungal meningitis from a steroid spinal injection. http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5149a1.htm
	• Injectable methylprednisolone and baclofen was recalled by FDA recommendation because of contamination with *Penicillium* mold, *Methylobacterium*, and/or *Mycobacterium chelonae*. This recall was later expanded to all products of Urgent Care Pharmacy due to poor manufacturing quality. https://scienceblog.com/community/older/archives/M/1/fda0779.htm
2001	• 11 patients contracted *Serratia marcescens* infections following the injection of betamethasone compounded at a community pharmacy in California. http://www.ncbi.nlm.nih.gov/pubmed/16941362
	• 4 children contracted *Enterobacter cloacae* infections from IV ranitidine compounded in a hospital pharmacy. http://www.ncbi.nlm.nih.gov/pubmed/12892028
	• 13 patients (3 fatalities) came down with bacterial meningitis after receiving contaminated betamethasone shots prepared by Docs Pharmacy in California. http://www.ashp.org/menu/News/PharmacyNews/NewsArticle.aspx?id=1125 http://www.sfgate.com/health/article/Steroid-meningitis-echoes-local-incident-3975723.php
	• Med-Mart Pulmonary Services of California was forced to recall five lots of Albuterol (an inhalant) due to contamination by *Serratia liquefaciens*. http://www.thefreelibrary.com/Letter+triggers+recall+for+compounding+pharmacy.+%28Human+Drugs%29.-a01040313332 http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2002/ucm145144.htm
1999	• Survey of compounded Alprostadil formulations from a variety of sources showed contamination in 18% of samples tested. http://www.ijpc.com/abstracts/abstract.cfm?ABS=684
1998	• 11 children became septic in California and 10 tested positive for *Enterobacter cloacae* bloodstream infections associated with contaminated prefilled saline syringes from CAPS, Braun-McGaw of Detroit, MI. (see also 2005 incident above). http://www.cdc.gov/mmwr/preview/mmwrhtml/00055644.htm
1990	• Four patients died of an *Enterobacter* infection from a filter-sterilized cardioplegia solution (a parenteral with high potential for bacteremia) compounded in a Nebraska hospital. In this episode five bottles of the solution tested were nonsterile, several subsequent bottles tested were sterile, and another 93 bottles were dispensed without being tested. http://drugtopics.modernmedicine.com/drugtopics/Health+System+News/USP-drug-safety-review-Requirements-for-compoundin/ArticleStandard/Article/detail/359826
	• 2 patients lost their vision after becoming infected by *Pseudomonas aeruginosa* found in indomethacin eye drops compounded in a Pennsylvania drug store. http://drugtopics.modernmedicine.com/drugtopics/Health+System+News/USP-drug-safety-review-Requirements-for-compoundin/ArticleStandard/Article/detail/359826
*All links confirmed 2/12/13	

of the polio scare, this vaccine exposed about 200,000 people to live us in the vaccine – 70,000 became ill and 200 were paralyzed with an additional 10 deaths.

The GMP has grown with FDA authority and in response to particular issues that have arisen. Validation of sterilization, change control, separation and product protection from cross-contamination with

penicillin, tamper-resistant closures, etc. are all addressed in the GMP in response to an issue in the marketplace.

This, then, is the purpose of GMP – a preventive system to create processes and procedures that assure consistently high quality drugs, along with reactive programs to promptly detect and then prevent recurrences of problems. It is against this background that we examine at what is going on in compounding pharmacies.

Compounding Pharmacies and Contamination Issues

The basic assumption in compounding pharmacies is that the pharmacist is creating a specific formulation in response to a doctor's script for a particular patient. This is a needed function in hospitals and street-corner pharmacies. However, it is not what is causing the problems we are reading about in the news. Some "pharmacies" are operating as pharmaceutical manufacturers, filling batches of thousands of units and then offering them for sale to doctors. These pharmacies, operating under widely varying standards frequently cite their lower costs over GMP manufactured medicines as a selling point. The potential issues this situation creates are obvious. It was precisely this type of situation that led to the generation of GMP.

This is not a small concern. According to a recent ISMP Medication Safety Alert [5]:

"The 2008 revision of the US Pharmacopeia (USP) Chapter <797> that left many facilities unable to meet the published standards for sterile compounding as well as the escalation in drug shortages have led to a steady increase in sterile compounding pharmacy services. A 2011 survey showed that 66% of hospital pharmacies outsource some portion of their sterile compounding. In some cases, pharmacists have purchased compounded products without full realization of the risks. An analysis of recent harmful cases of contaminated products from compounding pharmacies revealed breaches of USP <797>, unsafe staff behaviors, untrained and unskilled personnel, improper use of equipment, extended beyond use dating outside of manufacturer labeling without sufficient testing, and/or a lack of basic compounding skills involved in almost all cases. Outsourcing is also used as a cost-savings measure."

We had previous warnings about the dangers of conditions in compounding pharmacies. As early as 1976, the widespread contamination of medications from hospital pharmacies was reported in the literature (9% contamination rate of *P. aeruginosa* alone [6]). By the mid-1990s FDA was investigating a number of pharmacies that were operating as manufacturing facilities in response to a number of contamination events [7]. This situation led directly to the generation of USP chapter <1206> *Pharmacy Compounding Practices* in 1996. This was a non-mandatory chapter in USP and was provided for informational purposes.

These problems remain. In 2005 CDC investigated a multi-state outbreak of *Serratia marcescens* that was traced back to intravenous magnesium sulfate from a compounding pharmacy [8]. This outbreak provided additional impetus for the revision of USP sterile compounding guidance to the current version of USP <797> *Pharmaceutical Compounding – Sterile Preparations.*

Even later, an industry group conducted a survey on pharmacy practices that described widespread belief of contamination in sterile medications prepared by the pharmacies [9]. While the risk may not be as severe for a hospital pharmacy, compounding a specific medication for immediate administration, in a manufacturing environment the longer storage times may result in microbial proliferation and product spoilage [10]. This concern is supported by current events. For example, FDA reported in 2007 that the Agency had reports of 200 adverse events at that time involving 71 compounded products since 1990 [5]. To put these numbers in context, it should be noted that adverse event reporting is rare for pharmacy products. This is because, in contrast to products that are subject to approved drug applications, there are no adverse event reporting requirements for drugs made by pharmacies. The general public has been made aware of some examples as well – a few of which are outlined in Table 2. As you review these events, please also note that many involve shipment across state lines, and sometimes involve extremely large batch sizes.

USP and Compounding Pharmacies

The early history of USP parallels, in several respects, the recent contamination problems at NECC and the current state of regulation of compounding pharmacies. Early efforts (1790s-1810s) to create a pharmacopeia included the pharmacopeias of the College of Physicians (Philadelphia) and the Massachusetts pharmacopeia. However, not all of the newly-formed states adopted either of these pharmacopeias, which led to an effort to create a new pharmacopeia that enjoyed the support of all major medical societies and could serve as a "national" pharmacopeia. The first edition of this pharmacopeia was published in 1820. Throughout the 1800's the compendia was periodically revised, with the participation of pharmacists. The 1906 Pure Food and Drug Act specifically cited USP and the National Formulary (NF) as enforceable standards. The 1938 amendment to the FD&C Act established FDA as the empowered enforcement agency, and again cited USP and NF for standards [11].

Having had a quick look at the history of USP, where a multitude of state-level compendia led to uneven standards, allow us jump to the current time. USP <797> is the recognized standard of practice for compounding pharmacies manufacturing sterile products in the USA. While this standard is a huge improvement over the previous "best practice", it is far less stringent than the pharmaceutical GMP as described in 21 CFR 210/211. This is a point that must be remembered – USP <797> is clearly best practice among the top compounding pharmacies [12] but it is far less rigorous than the expectations of cGMP. This USP chapter's guidance is appropriate for small pharmacies servicing specific prescriptions (its intended use), but is not adequate for large-scale production of pharmaceutical batches.

USP first published information on sterile compounding in 1995 in chapter <1206> "Sterile Products for Home Use" in USP 23 [13]. This was a general informational chapter on compounding pharmacy and not as effective as was originally hoped [14]. In respose, USP changed the

informational chapter <1206> to the mandatory chapter <797> with the expectation that this change in status would allow enforcement of the provisions. It was also at this point that different levels of "sterile" were incorporated into the chapter [12]. These levels of sterility included low, medium and high risk products based on compounding process, product characteristics and storage conditions. [15]

This effort met with limited success. Voluntary compliance with USP and American Society of Hospital Pharmacies (ASHP) was low – estimated at 5.2% in a 2003 industry survey [12].

There were several "GMP"-like requirements that were new to the compounding pharmacy. Examples include the requirement for robust ISO Class 5 fill conditions, as well as the contamination control, facility, environmental monitoring, personnel gowning and training requirements.

However, these changes were not sufficient to address the continuing problems with compounding pharmacy Quality issues. In one case, for example, a "for cause" type of inspection ran into difficulty as the inspector objected to the lack of any written procedures. In reply, the pharmacist challenged the inspector to show any such requirement. This, and similar, experiences led to the revision of USP <797> in 2009 to incorporate several additional Quality controls [16].

It is interesting to note that at the time of this writing, there remain no uniform expectations for observance of USP <797> requirements and in fact the best estimate is that only 23 states currently require compliance with USP <797> [17]. A recent review article also highlighted the uneven training of pharmacists in the expectations of USP <797> [18]. Finally, we must remember that in comparison to cGMP, USP <797> Quality and safety standards are relatively lax as the expectation is that the medicine will be used immediately on a particular patient under a doctor's specific direction. This is not the target market for the large compounding pharmacies like Massachusetts' now bankrupt NECC.

FDA & Compounding Pharmacies

Although FDA asserts jurisdiction over compounding pharmacies, as a practical matter, the stated policy of the Agency has been to restrict its attention to large-scale manufacturing in "compounding pharmacies" rather than the traditional creation of a specific formulation in response to a doctor's prescription for a specific patient. As noted in a 2003 GAO report:

"FDA and others have also expressed concern about the potential for harm to the public health when drugs are manufactured and

distributed in commercial amounts without FDA's prior approval. While FDA has stated that traditional drug compounding on a small scale in response to individual prescriptions is beneficial, FDA officials have voiced concern that some establishments with retail pharmacy licenses might be manufacturing new drugs under the guise of drug compounding in order to avoid FDCA requirements." [19]

The concerns expressed by FDA were accurate, although this should be of little surprise given the history of FDA as the national guardian of safe medications. The situation, where a patchwork of state regulations and enforcement capabilities addresses compounding pharmacy practices, lends itself to uneven effectiveness. For example, in a 2003 testimony it was related that North Carolina has six inspectors for 2,000 pharmacies and claimed each was inspected at least every 18 months (this assertion works out to 1 inspector for every 333 pharmacies, with a work load of 19.5 pharmacy inspections with associated paperwork/ month – unless the inspector has field complaints to investigate, which take priority over inspections) [19].

This patchwork of regulation remains. The National Association of Boards of Pharmacy (NABP) relates that currently:

"...at least 23 states require compliance with USP <797>... and seven additional boards indicate that they have rules that include some or most of the USP Chapter 797 standards. Three boards of pharmacy have such regulations pending, and another has regulations under consideration. In addition, Hawaii considers compliance with USP Chapter 797 a standard of practice, and the South Carolina Department of Labor, Licensing, and Regulation – Board of Pharmacy indicates that they have publically instructed licensees that it considers compliance with USP Chapter 797 to be appropriate professional practice and that it will consider serious deviation to be grounds for discipline." [17]

As was described above, USP has been working to develop enforceable guidance for compounding pharmacies in chapters <795> and <797> [12] but as of the time of this writing, state boards of pharmacy have yet to consistently include these expectations in their local standards [17]. Even in states that do include them, it is unclear whether the states have the resources to enforce the regulations [20]. This concern is supported by data. In a recent series of unannounced inspections by the Massachusetts' Board of Pharmacy in the wake of the NECC scandal [21], only 4 of 40 compounding pharmacies met expected standards [22]. Eleven pharmacies were issued immediate cease and desist orders.

In a revealing letter to FDA, the American Society of Health-System Pharmacists (ASHP) argues against unfettered FDA oversight of large pharmacies arguing that they are a necessary part of American pharmaceutical service and should not be impeded [23]. Their position is stated as:

"ASHP has long recognized that hospitals may also enlist the help of qualified compounding pharmacies for some compounded preparations for several reasons. For example, they may not have necessary equipment or facilities to prepare some high-risk preparations, or they may face medication shortages for commercial products that can only be replicated by a compounding pharmacy.

The Society's policy position on compounding (excerpted) is as follows:

- To affirm that extemporaneous compounding of medications, when done to meet immediate or anticipatory patient needs, is part of the practice of pharmacy and is not manufacturing;
- To encourage pharmacists who compound medications to use only drug substances that have been manufactured in Food and Drug Administration-approved facilities and that meet official United States Pharmacopeia (USP) compendial requirements where those exist;
- To encourage unaccredited facilities where extemporaneous compounding of medications occurs to seek accreditation by a nationally credible accreditation body;
- To advocate the adoption, in all applicable state laws and regulations governing health care practice, of the intent of the requirements and the outcomes for patient safety as described in United States Pharmacopeia Chapter 797."

In other words, large scale compounding is required because smaller facilities may not have the expertise to make sterile products, and GMP facilities may have shortages. ASHP encourages (but does not support requiring) its members to meet USP <797> standards. The letter continues later:

"A sterile compounding business entity that does not fill prescriptions for individual patients is not a pharmacy. Regulatory oversight of these entities should be dependent on the scope and scale of their operations, which may range from patient-specific small batches to large-scale production of commonly used drugs or formulations based on historical demand. The beyond use date (BUD) or shelf life these entities assign to final products as well as the risk level (low, medium, high) of the compounding activity are also factors.

ASHP believes that the FDA has limited authority to inspect large scale compounding entities since most are licensed and operating as pharmacies. We believe that FDA's authority needs to be clarified or new authorities given to FDA to regulate compounding businesses that produce large amounts of compounded products, and sell those products to entities other than the end user. ...

The Society believe *[sic]* that compounding service providers that operate at the scale and scope of manufacturers should be required to register with the FDA, share details about their operations with the Agency, and submit to routine inspections." [23]

While this last paragraph is encouraging, it seems clear that the safety of the public demands a nationally directed enforcement of GMP on all large-scale pharmaceutical manufacturers, even the ones who have been classified as compounding pharmacies.

Conclusions

GMP may be, at times, difficult to maintain, and sometimes seem overly proscriptive, but it provides a common set of expectations for the establishment and maintenance of controls over product Quality that require care and attention. It is vastly superior to the dangers

of unregulated pharmaceutical products. In an industry dependent on trust, manufacturers and the public both need come commonly accepted practices to guide production as well as someone to police the less educated and prepared manufacturer. This is a national, not a state, issue as the medicines are shipped nationwide where they are needed. We have to be able to have confidence in the strength, quality and safety of our medicines. GMP is the rulebook by which this confidence is encouraged. The dangers of unregulated (or under-regulated) production of medicines for national distribution are obvious in the news.

Author Biography

***Scott Sutton, Ph.D.**, is the Principal of Microbiology Network, Inc. (http://www.microbiologynetwork.com), a company he started in 1996 as a means to encourage training and communications within the microbiological community. He is a recognized consultant and trainer with emphasis in GMP, investigations, Environmental Monitoring and contamination control (both Aseptic manufacturing and non-sterile production facilities) as well as microbiology laboratory audits and operations. The Microbiology Network supplies consulting, training, webinars and e-mail discussion groups. Dr. Sutton is an active author and speaker for the industry, supports PDA and has served with the USP Analytical Microbiology Committee of Experts since 1993. He may be reached at scott.sutton@microbiol.org.*

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IN THE MATTER OF	*	**BEFORE THE**
CENTRAL ADMIXTURE PHARMACY	*	**MARYLAND**
SERVICES, INC.	*	**STATE BOARD**
License Nos.: PW0184/D01075	*	**OF PHARMACY**
Respondent-Pharmacy/Distributors	*	

* * * * * * * * * * * *

CONSENT ORDER

Based on information received and a subsequent investigation by the State Board of Pharmacy (the "Board"), and subject to the Maryland Pharmacy Act (the "Act"), Md. Health Occ. Code Ann. (H.O.) §§ 12-101, et seq., (2005 Repl. Vol.), the Board issued an Order for Summary Suspension dated November 15, 2005, which summarily suspended the pharmacy and distributor permits issued to Central Admixture Pharmacy Service Inc., (the "Respondent-Pharmacy"). Specifically, the Board found that the public health, safety or welfare imperatively required emergency action, pursuant to Md. St. Gov't Code Ann. § 10-226(c)(2) (2004 Repl. Vol.). The Board also had cause to believe that the Respondent-Pharmacy had violated the following provisions of H.O. § 12-409:

> (a) *In general.* - Subject to the hearing provisions of § 12-411 of this subtitle, the Board may suspend or revoke any pharmacy permit, if the pharmacy:
> (1) Is conducted so as to endanger the public health or safety;
> (2) Violates any of the standards specified in § 12-403 of this subtitle; or
> (3) Otherwise is not conducted in accordance with the law.

The Board also had cause to believe that the Respondent-Pharmacy violated H.O. § 12-403, which provides:

§ 12-403 Required Standards

(b) In general. – Except as otherwise provided in this section, a pharmacy for which a pharmacy permit has been issued under this title:

(1) Shall be operated in compliance with the law and with the rules and regulations of the Board.

(2) Shall be located and equipped so that the pharmacy may be operated without endangering the public health or safety.

Additionally, the Board also had cause to believe that the Respondent-Pharmacy violated Code Md. Regs. Tit. 10, § 34.19.03, which states in relevant part:

.03 Pharmacy Environment

In addition to all statutes, laws and regulations applicable to all pharmacies operating under permits issued by the Board of Pharmacy, a pharmacy engaged in the compounding and dispensing of sterile parenteral/enteral prescription preparations within a pharmacy shall maintain an environment for this practice which is set apart, and is designed and equipped to provide controlled aseptic conditions.

The Respondent-Pharmacy was given notice of the Order for Summary Suspension by letter dated November 16, 2005.

The parties and the Board agreed to resolve the matter by way of settlement. As a result of negotiations, the Respondent-Pharmacy agreed to enter into this Consent Order, consisting of Findings of Fact, Conclusions of Law and Order.

FINDINGS OF FACT

1. At all relevant times, the Respondent-Pharmacy[1] was authorized to operate a pharmacy and distribute prescription drugs in the State of Maryland. The Respondent-Pharmacy was first issued a permit to operate a pharmacy on March 25, 1999, under permit number PW0184, and a permit to distribute prescription drugs on March 26, 1999, under permit number D01075.

[1] CAPS operates multiple pharmacies across the United States. All references to CAPS in this order are to its Lanham, Maryland facility unless otherwise noted.

2. At all relevant times, the Respondent-Pharmacy was operating a pharmacy and distributing prescription drugs at 9730 Martin Luther King Jr. Highway, Lanham, Maryland 20706.

3. The Respondent-Pharmacy admixes, dispenses and delivers labeled, patient specific and anticipatory Intravenous ("IV") prescriptions to patients and hospitals in the District of Columbia, Delaware, Virginia, and Maryland. Among the many products the Respondent-Pharmacy produces are an array of cardioplegia solutions ("Cardioplegia") that are administered to patients during heart by-pass surgery to stop the beating heart.

4. On or about September 12, 2005, the Board received a complaint concerning a series of cases involving "systemic inflammatory response syndrome" ("SIRS") that had taken place in open-heart surgery patients at Mary Washington Hospital in Virginia. The Board's investigator was informed that the patients suffering from SIRS had received Cardioplegia during open-heart surgery that was compounded by the Respondent-Pharmacy. The Board makes no finding of fact as to any direct relationship between CAPS' Cardioplegia and any patient injury at Mary Washington Hospital.

5. On or about September 12, 2005, the Food and Drug Administration's ("FDA") Baltimore District Office began an investigation into the reported cluster of SIRS cases at Mary Washington Hospital. The FDA also concurrently inspected the Respondent-Pharmacy's facility in Lanham, Maryland and discovered significant Good Manufacturing Product violations, specifically stating that there was no assurance of sterility of any of the Respondent-Pharmacy's manufactured products.

6. On or about September 16, 2005, the FDA contacted the Board to inform it that, following its preliminary investigation, the FDA had: (1) stopped shipment of all products manufactured at the Respondent-Pharmacy's Lanham, Maryland facility; (2) required the Respondent-Pharmacy to notify customers of all products to quarantine and/or hold all product(s) until further notice; and (3) required the Respondent-Pharmacy to issue a press release concerning the situation.

7. On or about September 16, 2005, the Respondent-Pharmacy issued an "Urgent Drug Recall" notification to its customers for all injectable products manufactured at the Lanham, Maryland facility. Additionally, the Respondent-Pharmacy, at the Board's request, voluntarily ceased distributing and dispensing all prescription products from the Lanham, Maryland facility.

8. On or about September 16, 2005, the FDA received lab results from its New York Regional Laboratory ("NRL"). Preliminary test results of some intact Cardioplegia samples collected from Mary Washington Hospital exhibited the presence of bacteria.

9. On or about September 19, 2005, the FDA reviewed records at the Respondent-Pharmacy facility documenting that the hood the Respondent-Pharmacy uses for the manufacture of Cardioplegia was found positive for bacterial growth last year during the firm's environmental testing.

10. On or about September 20, 2005, the FDA received a report from Sinai Hospital in Baltimore, Maryland concerning a patient who was administered Cardioplegia compounded by the Respondent-Pharmacy on September 11, 2005, post-

operatively. The Board makes no finding of fact concerning any direct relationship between any patient injury at Sinai Hospital and CAPS' Cardioplegia.

11. The Cardioplegia administered to patients at Mary Washington Hospital consists of three solutions.[2] Each patient received one bag of each solution during surgery. Solutions One and Two have different levels of potassium and are used during surgery. Solution three is a warmed solution that is used at the end of surgery. Upon testing, Mary Washington Hospital found bacteria in an intact IV bag of solution Two.[3] Furthermore, testing by the FDA's North Regional Laboratory detected the presence of bacteria in intact IV bags of Cardioplegia from both Mary Washington Hospital and Sinai Hospital.

12. The production of Cardioplegia and other patient specific and anticipatory IV drug products require the strict adherence to aseptic sterile techniques.

13. On or about October 12, 2005, the FDA issued a list of Inspectional Observations to the Respondent-Pharmacy, finding the Respondent-Pharmacy failed to meet the standards required by United States Pharmacopeia ("USP"), Chapter 797. The FDA reviewed product preparation and processing at the Respondent-Pharmacy on or about September 13, 14, 15, 19, 20, and October 5, 11, 12, 2005, and made the following observations:

a. Information received during the inspection indicates that the firm has not designated any staff member or multiple staff members at this location to be part of a Quality Control Unit (QCU);

[2] The Cardioplegia at Mary Washington Hospital was manufactured per the hospital's instructions. The pertinent date codes at this time consist of Cardioplegia manufactured by the Respondent-Pharmacy on August 11, 2005 and August 30, 2005.
[3] This testing was performed on or about September 11, 2005.

b. Sterility testing is not performed for infusion products produced by the firm with twenty-four (24) to thirty (30) day expiration dates (for example, Dialysate, Oxytocin, Magnesium) produced by the firm;

c. Infusion/Injectable products are not always labeled as sterile;

d. Employees did not follow proper gowning procedures;

e. Sterile parenteral products made by the firm are not always kept at appropriate temperatures during shipping;

f. CAPS has not sent out one sample from each of the environmental monitoring tests for speciation each quarter;

g. No specific instructions are provided for the location of weekly surface touch plate monitoring;

h. Positive and negative controls are not run concurrently with each microbiological environmental monitoring test;

i. Production areas (Class 100 hoods) have not been qualified under dynamic conditions to assure that unidirectional airflow sweeps any potential contamination away from the product;

j. CAPS Standard Operating Procedures (SOP) fails to address the frequency of calibration of the thermometers used to monitor the temperature in CAPS' refrigerators, freezers, production rooms and incubators where components and products are stored. Likewise, there is no documentation demonstrating that the thermometers were properly calibrated;

k. Documentation of the calibration of several of the balances used in the production of parenteral drug products indicated that the balances were found by the contractor to be out of calibration. There is no documentation indicating that the out-of-specification results were investigated to determine if there was an effect on the product. Likewise, CAPS' SOP fails to provide corrective action for out-of-specification results;

l. Employees routinely involved in the production of parenteral drug products made by CAPS lacked intial and/or annual aseptic and gowning training and/or there was inadequate documentation reflecting that such training had occurred;

m. The Director of Pharmacy is not performing or documenting a monthly review of environmental logs;

n. Required cleaning log sheets are not always completed and the monthly review of the cleaning log sheets is not always conducted; and

o. CAPS uses unapproved forms and/or fails to document the lot numbers of all the components brought into the production room each day.

p. While CAPS has a manual of SOPs in place concerning Quality Control, Gowning Requirements, Environmental Monitoring, Training Policy, Room Cleaning and Documentation, TPN and Cardioplegia Compounding Procedure, it fails to follow the requirements of the same.

14. Additionally, information provided by the FDA and the Respondent-Pharmacy demonstrated that recent environmental testing performed at the Respondent-Pharmacy's facility showed the presence of bacteria in a water container used for cleaning, additive port tube holders, and spray bottles filled with sterile water. Likewise, sterility testing demonstrated similar bacteria in its drug products.

15. Based on the above investigative facts, the Board contracted the services of an independent expert in compounding/infusion pharmacy (hereinafter "Board Expert") to conduct a review of the investigative findings of the Respondent-Pharmacy's practices. The practices affected the production of Cardioplegia and the patient specific and other anticipatory IV drug products produced by the Respondent-Pharmacy at its Lanham facility. Furthermore, the practices and information raised sterility concerns about Respondent-Pharmacy's facility and its drug products.

16. Based on a review of the documents relating to the FDA's inspection and observations as well as the documents turned over to the Board by the Respondent-Pharmacy, the Board concluded that the Respondent-Pharmacy was not operating within the standards required of an aseptic facility suitable for the compounding of patient specific and anticipatory IV drug products. The Board concluded that the Respondent-

Pharmacy's operation of a pharmacy posed a risk to the public health, safety, or welfare imperatively requiring emergency action and summarily suspended the Respondent-Pharmacy's pharmacy permits.

CONCLUSIONS OF LAW

Based upon the foregoing Findings of Fact, the Board finds that Respondent-Pharmacy violated Md. Health Occ. Code Ann. § 12-409(a)(1) – (3), § 12-403(b)(1) and (2), and COMAR 10.34.19.03.

ORDER

Based on the foregoing Findings of Fact, Conclusions of Law and agreement of the parties, it is this 10th day of January, 2006 by a majority of a quorum of the Board,

ORDERED that the suspension shall be continued and the Respondent-Pharmacy shall remain closed and all operations related to the operation of a pharmacy and distribution of prescription drugs in the State of Maryland shall remain discontinued; and it is further

ORDERED that the Respondent-Pharmacy may be reinstated, such reinstatement to be conditioned upon completion of the following terms and conditions, and upon the filing of a petition for reinstatement:

1. The Respondent-Pharmacy shall implement a corrective action plan, which includes (a) revisions to the Respondent-Pharmacy's procedures and quality assurance plan and (b) adequate safeguards for the Respondent-Pharmacy to reopen without posing a threat to the safety and health of the public;

2. The Board will review the Respondent-Pharmacy's corrective action plan and operations to determine if the Respondent-Pharmacy has an adequate corrective action plan and has implemented the corrective action plan to the Board's satisfaction;

3. If the Board determines that the corrective plan or its implementation is not adequate, it will promptly notify the Respondent-Pharmacy to enable it to revise or amend the corrective action plan as appropriate; and

4. The Respondent-Pharmacy may petition the Board for reinstatement. If the Board is satisfied that the Respondent-Pharmacy has demonstrated to the Board a sufficient corrective action plan is in place and has been adequately implemented in its Lanham facility, the Board will, in accordance with the terms and conditions of this Consent Order, reinstate the Respondent-Pharmacy and approve the Respondent-Pharmacy to reopen; and it is further

ORDERED that this Consent Order is effective as of the date of its signing by the Board; and it is further

ORDERED that the Respondent-Pharmacy shall comply with all laws governing the operation of a pharmacy and the distribution of prescription drugs; and it is further

ORDERED that the Respondent-Pharmacy shall be responsible for all costs incurred under this Consent Order; and it is further

ORDERED that for purposes of public disclosure, as permitted by Md. State Gov't Code Ann. § 10-617(h) (2004 Repl. vol.), this document consists of the contents of the foregoing Findings of Fact, Conclusions of Law and Order and that the Board may disclose the contents of this Consent Order to any mandatory reporting data bank(s) that it is required to.

JAN 1 0 2006

~~John H. Baleh~~ Jeanne Furman
~~President~~ Secretary
Maryland State Board of Pharmacy

CONSENT OF CENTRAL ADMIXTURE PHARMACY SERVICES, INC.

I, Thomas J Wilverding, a duly authorized representative of the Respondent-Pharmacy and on behalf of same, affixing my signature hereto, acknowledge that:

I am represented by my attorney, Constance H. Baker, Venable LLP, and have consulted with counsel before entering this Consent Order. By this Consent and for the purpose of resolving the issues raised by the Board, I agree and accept to be bound by the foregoing Consent Order and its conditions.

I acknowledge the validity of this Consent Order as if entered into after the conclusion of a formal evidentiary hearing in which I would have had the right to counsel, to confront witnesses, to give testimony, to call witnesses on my own behalf, and to all other substantive and procedural protections provided by the law. I agree to forego my opportunity to challenge these allegations. I acknowledge the legal authority and jurisdiction of the Board to initiate these proceedings and to issue and enforce this Consent Order.

By entering into this Consent Order, I acknowledge that the failure to abide by the conditions set forth in this Consent Order and following proper procedures, the Respondent-Pharmacy may suffer disciplinary action, possibly including revocation, against its permit to operate a pharmacy and distribute prescription drugs in the State of Maryland.

I sign this Consent Order after having an opportunity to consult with counsel, voluntarily and without reservation, and I fully understand and comprehend the language, meaning and terms of the Consent Order.

12/27/05
Date

Central Admixture Pharmacy Services, Inc.

STATE OF MARYLAND)
) to wit:
CITY OF)

I HEREBY CERTIFY that, on this 27 day of December, 2005 before me, the subscriber, a Notary Public of the State and City aforesaid, personally appeared Thomas Wilkerding, and he/she acknowledged the foregoing to be his act and deed.

AS WITNESS my hand and Notarial Seal.

Angelia L Warn
Notary Public

My Commission Expires: 11/10/2009

B. Braun Medical Inc 15-Mar-06

Department of Health and Human Services

Public Health Service
Food and Drug
Administration

PHILADELPHIA DISTRICT
900. U.S. Customhouse
2nd and Chestnut Streets
Philadelphia, PA 19106
Telephone: 215-597-4390

WARNING LETTER
06-PHI-03

CERTIFIED MAIL RETURN
RECEIPT REQUESTED

March 15, 2006

Caroll H. Neubauer
Chairman and Chief Executive Officer
B. Braun Medical Inc.
824 Twelfth Avenue
Bethlehem, PA 18018

Dear Mr. Neubauer:

This Warning Letter concerns drug preparation activities performed by Central Admixture Pharmacy Services (CAPS), a subsidiary of B. Braun Medical Inc. (B. Braun). In particular, this Warning Letter concerns **[redacted]** solutions produced by CAPS at its facility produced by CAPS at its facility in Lanham Maryland, **[redacted]** produced by CAPS at its facility in Santa Fe Springs, California, and other drugs produced by CAPS at its facilities in: Homewood, Alabama; Lanham, Maryland; Horsham, Pennsylvania; and Kansas City, Missouri.

Your **[redacted]** solutions, **[redacted]**; and other products prepared at your facilities are drugs within the meaning of section 201(g)(1) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 321(g)(1)) ("the Act" or "FDCA"). These products are new drugs under section 201(p) of the Act (21 U.S.C. § 321(p)) because they are not generally recognized by qualified experts as safe and effective for their labeled uses As discussed below, these drugs and your, production and distribution of these drugs violate the Act.

Factual Background

On September 12, 2005, the Virginia Department of Health and the Centers for Disease Control and prevention (CDC) notified FDA that **[redacted]** patients at **[redacted]** in developed a severe systemic inflammatory response after **[redacted]**. All of these patients received **[redacted]** solutions made by CAPS Lanham, MD facility. **[Redacted]** of these patients **[redacted]** and the other **[redacted** after bein

treated. CDC and the Virginia Department of Health reported that **[redacted]** of the **[redacted]** patients received the **[redacted]** solutions in late August or early September.

On September 12, 2005, FDA investigators initiated an investigation at **[redacted]** FDA and CDC initial sults from testing of unopened bags of **[redacted]** solutions made by CAPS at the Lanham, MD facility and collected from **[redacted]** indicated the presence of **[redacted]**.

On September 16, 2005, after discussion with FDA, CAPS Lanham, MD voluntarily notified all customers who had purchased products from them to immediately examine their inventory and quarantine all products made by CAPS at this facility. CAPS notified over **[redacted]**hospitals and suspended distributio of all injectable products pending the investigation.

On September 19, 2005, FDA laboratory analysis confirmed the presence of several species of **[redacted** in unopened samples of **[redacted]** solutions collected from **[redacted]**.

On September 20, 2005, FDA received a MedWatch report from **[redacted]** in **[redacted]** concerning a patient who developed **[redacted]**with **[redacted]** after receiving **[redacted]** solutions prepared by CAPS at the facility in Lanham, MD. FDA collected from **[redacted]** unopened bags of **[redacted]** solutions made by CAPS at the facility in Lanham, MD facility. FDA's laboratory results from testing the **[redacted]** solutions indicated the presence of several species of **[redacted]**.

Prior to the reports received by FDA regarding **[redacted]** drugs produced by CAPS, FDA investigators had inspected the CAPS facility located at 10370 Slusher Drive, Suite 6, Santa Fe Springs, CA, in November 2004. This November 16, 2004 inspection revealed that CAPS produces and distributes **[redacted]** for further manipulation by hospital pharmacies. An FDA approved **[redacted]**product is commercially available.

Subsequent to the reports, FDA inspected CAPS facilities in Homewood, AL, Lanham, MD, Horsham, PA, and Kansas City, MO in September and October, 2005.

On November 3, 2005, FDA met with representatives of CAPS to discuss FDA's concerns regarding the,compounding activities of CAPS.

Compounded Drugs under the FDCA and FDA's Regulatory Approach to Compounding

FDA regards traditional pharmacy compounding as the combining, mixing, or altering of ingredients by a pharmacist in response to a physician's prescription to create a medication tailored to the specialized needs of an individual patient. See *Thompson v. Western States Med. Ctr.*, 535 U.S. 357, 360-61 (2002). When a pharmacist compounds a drug, by definition, he or she creates a "new drug" under the FDCA because the compounded product is not "generally recognized, among experts...as safe and effective." Cf. 21 U.S.C. §§ 321(p) and 321(v)(1); *Hynson, Westcott & Dunning v. Weinberger*, 412 U.S. 609, 619, 629-3 (1973) (stating that unique, customized compounded drugs cannot be generally recognized as safe and effective). Under the FDCA, any new drug may not be legally introduced, or delivered for introduction, int interstate commerce unless FDA approves the drug as safe and effective in an application (21 U.S.C. § 355).

FDA has long recognized, however, that traditional pharmacy compounding serves an important public health function. Accordingly, FDA historically has not taken enforcement actions against pharmacies engaged in traditional pharmacy compounding.1 Rather, FDA has directed its enforcement resources against establishments that manufacture large quantities of unapproved new drugs in the guise of traditional compounding or whose compounding practices pose a significant or immediate threat to the public health or to the integrity of the drug approval process of the FDCA. FDA's current enforcement policy with respect to pharmacy compounding is articulated in Compliance Policy Guide (CPG), section 460.200 ["Pharmacy Compounding"] (May 2002), which is attached to this letter. The CPG contains factors that the agency- considers in deciding whether to exercise its enforcement discretion. The factors identified in the CPG include whether a pharmacy is:

- compounding drugs in anticipation of receiving prescriptions, except in very limited quantities in relation to the amounts of drugs compounded after receiving valid prescriptions; and
- compounding drugs that are commercially available in the marketplace or that are essentially copies of commercially available FDA-approved drug products.

The factors listed in the CPG are not intended to be exhaustive and other factors may also be appropriate for consideration.

As was discussed during the November 3, 2005, meeting, and as specified below, we are seriously

concerned with the public health risks posed by your compounding of contaminated drugs and compounding practices. All of the CAPS facilities that were inspected distribute **[redacted]** of compounded prescription drugs to hospitals without patient prescriptions, and without assurance that the **[redacted]** of contracted hospitals have in place the necessary controls to link your prescription products , lot, control numbers, or otherwise, to specific patients. FDA's willingness to exercise enforcement discretion regarding your anticipatory compounding of drugs is dependent on CAPS's ability to link its compounded drugs to the specific patients to whom the drugs are ultimately dispensed. In addition, as described below, FDA is concerned with your compounding of drugs that are copies of commercially available FDA-approved drugs.

C. Adulterated [redacted] Solution- Product Contamination

The FDA has determined that several lots of **[redacted]** solutions produced by CAPS at the facility in Lanham, MD are adulterated within the meaning of Sections 501(a)(1) of the Act (21 U.S.C. §§351(a)(1)), in that several intact units of CAPS **[redacted]** solutions were determined to be contaminated with **[redacted]**. In addition, these **[redacted]** solutions are adulterated within the meaning 501(c) of the Act (21 U.S.C. § 351(c)), in that their purity or quality falls below that which they purport or represent to possess. These **[redacted]** solutions produced by CAPS at the facility in Lanham, MD are not **[redacted]**

As stated above, FDA laboratory analysis confirmed the presence of several species of **[redacted]** including **[redacted]** and/or **[redacted]**in unopened samples of **[redacted]** solutions produced by CAPS at the facility in Lanham, MD and collected from **[redacted]** and **[redacted]**. In addition, the CDC and Mary Washington Hospital have independently tested and confirmed that unit of CAPS **[redacted]**solution produced by' CAPS at the facility in Lanham, MD were contaminated. CAPS has also advised FDA that it confirmed the presence several **[redacted]** (e.g. **[redacted]**) intact units of finished **[redacted]** solutions produced by CAPS at the facility in Lanham, MD.

D. Adulterated Drugs - Insanitary Conditions and Current Good Manufacturing Practice Deficiencies

Your **[redacted]** solutions and other sterile drug products are adulterated within the meaning of Section 501(a)(2)(A) of the Act ((21 U.S.C . § 351(a)(2)(A)) in that they were prepared, packed, or held under in ilitary conditions whereby they may have been contaminated with filth, or whereby they may have beer rendered injurious to health. Additionally, your **[redacted]** solutions and other sterile drug products are adulterated within the meaning of Section 501(a)(2)(B) of the Act (21 U.S.C. § 351 (a)(2)(13)), because the methods used in, or the facilities or controls used for, the preparation of sterile drugs do not comply with current good manufacturing practice to assure that these drug products, meet the requirements of th Act as to safety and have the identity and strength, and meet the quality and purity characteristics, which they purport or are represented to possess.

During the inspections of CAPS facilities in Homewood, AL, Lanham, MD. Horsham, PA, and Kansas City, MO in October 2005. FDA Investigators observed numerous practice that deviate from the acceptable standards for the preparation of sterile drugs including:

During the inspections of CAPS facilities in Homewood, AL, Lanham, MD, Horsham, PA, and Kansas City, MO in October 2005, FDA investigators observed numerous practices that deviate from the acceptable standards for the preparation of sterile drugs including:

1. Failure to appropriately train and qualify personnel who perform critical tasks during the production of sterile drug products that require proper aseptic processing technique. (Investigators observed this deviation during the inspections of CAPS facilities in Lanham, MD; Homewood, AL; Horsham, PA; and Kansas City, MO.)

Specifically, at all of these facilities, several employees touched nonsterile surfaces with the sterile surfaces of their gloves, walked from the"dirty" side of the gowning suite to the "clean" side without shoe covers, and only partially donned shoe covers and hair nets. One employee at the CAPS facility in Kansas City, MO was smoking outside of the facility, while still wearing the clean .room gown, and then re-entered the **[redacted]** area without changing his gown. Also, an employee at the CAPS facility in Homewood, AL performed aseptic manipulations while his head, arms, and entire upper torso were tructing the unidirectional air flow within the **[redacted]**. This unidirectional air flow is meant to prevent any foreign particulates from contaminating the sterile drugs that are prepared within the hood. Another employee at the CAPS facility in Horsham, PA used the critical surfaces of the **[redacted]**as a writing surface while preparing sterile drugs. His head was obstructing the unidirectional air flow within the hood and his forearms were resting on the work area within the hood where aseptic manipulations are performed.

Also, several employees at the CAPS facilities in Lanham, MD, Homewood, AL, and Kansas City, MO have not been **[redacted]** re-trained on aseptic technique and gowning operations, as stated in the CAPS written procedure, **[redacted]**. In addition, some employees at the facilities in Lanham, MD, and Homewood, AL had been compounding sterile preparations for over **[redacted]** prior to receiving the proper annual re-training.

We acknowledge your November 25, 2005, response which states that appropriate CAPS. personnel have now been re-trained, however, the specific elements of your re-training program were not described in your response. We believe that a thorough training program includes topics such as aseptic technique, clean room behavior, microbiology, hygiene, gowning, and patient safety hazards posed by a non-sterile preparation.

Please describe the specific topics that were included in your training program for employees.

2. Failure to adequately assess and monitor the aseptic environment where you produce medium and high risk sterile preparations. (Investigators observed this deviation during the inspections of CAPS facilities in Lanham, MD, Homewood, AL, Horsham, PA, and Kansas City, MO.)

Specifically, the environmental monitoring procedures at CAPS facilities in Lanham, MD, Homewood, AL, and Horsham, PA do not state the locations where touch plate monitoring samples should be taken. During the inspection, CAPS states that it did not know whether samples were taken from the critical sites in the compounding process (i.e., from high traffic areas or areas that are hard to clean). At the CAPS facility in Kansas City, MO, the procedures for personnel monitoring only require **[redacted]** but do not include other potentially critical sites, such as the forearms. Also, environmental monitoring is performed only on **[redacted]** at the CAPS facility in Kansas City, MO, although compounding operations are less frequent than on weekdays. During the inspection, CAPS agreed that the weekend operations were not as intensive as weekday operations, and did not accurately represent a typical weekday production scenario for performing environmental monitoring.

The FDA believes that an effective environmental monitoring program should carefully select sampling location, timing, and frequency based upon their relationship to the operation performed. Samples should be taken throughout the aseptic processing area using scientifically sound sampling procedures.

Your November 25, 2005, response states that your written procedures would be revised, to include more details of environmental sampling locations. You have also added the testing of the **[redacted]** from each **[redacted]** to the environmental monitoring at your facilities. Your revised procedures do not instruct employees to specifically record which forearm, hand; or finger is tested on each environmental monitoring sample. Additionally, you stated that environmental monitoring will be performed during times of **[redacted]** and **[redacted]**.Your corrective actions will be evaluated during next inspection of your facilities.

Written corporate procedures for environmental monitoring did not require testing of **[redacted]** and **[redacted]** controls as part of the analysis for environmental monitoring samples. Your November 25, 2005, response states that environmental monitoring media is received at a **[redacted]** . Your response further clarified that CAPS will institute a **[redacted]**. Please state how frequently this test will be conducted and whether it will be applied as part of the analyses for all environmental monitoring samples

3. Failure to assure that equipment, apparatus, and devices used to produce your sterile preparations are consistently capable of operating properly and within acceptable tolerance limits. (This observation was noted during the inspections of CAPS facilities in Lanham, MD, Homewood, AL, Horsham, PA, and Kansas City, MO.).

Specifically, your firm has failed to assure proper calibration and maintenance of the thermometers, balances, and other equipment that are commonly used to support the compounding operations for your sterile products, as follows:

- At the CAPS facilities that FDA inspected, CAPS does not routinely calibrate thermometers that monitor the temperature in refrigerators, freezers, production rooms, and incubators where components and products are stored. CAPS written procedures did not address the calibration frequency or specifications for these instruments.
- At the CAPS facility in Kansas City, MO, **[redacted]** used to monitor **[redacted]** and **[redacted]** in admixed parenteral **[redacted]** formulations and other admixed prescriptions, was not calibrated in the 2nd Quarter of 2005. CAPS written procedures require that this instrument be calibrated on a **[redacted]** basis.

- At the CAPS facilities in Lanham, MD and Homewood, AL facilities, personnel knowingly utilized during the compounding of sterile preparations several balances that were between **[redacted]** and **[redacted]** out of calibration at the **[redacted]** test weight. Furthermore, CAPS did not investigate any of these deviations to determine if there was any effect on the final product. In fact, your written procedures do not discuss initiating an investigation to determine whether product may have been impacted, nor discuss corrective actions for equipment that does not meet acceptable tolerance limits.

Your November 25, 2005, response states your written procedures have been updated to include **[redacted]** traceable thermometers as part of a "re-certification" schedule. Your response further stated that the thermometers would be calibrated at two temperatures. Please clarify which specific temperatures will be used in the thermometer calibration. Also, please justify your rationale in establishing this operating range for the thermometers.

Regarding the calibration of balances, your November 25, 2005, response stated that an investigation into potential product impact was performed at Lanhani, MD, and Homewood, AL, but it was never documented. Your response further clarified that your firm determined that "the deviations were within normal pharmacy compounding practices . . ." and that the deviations "are not clinically significant. . . ." Additionally, your November 25, 2005, response stated that your firm will complete an investigation and corrective action report by November 30, 2005 for the balances that did not meet acceptable tolerance limits. In your December 12, 2005, response, you provided a copy of the completed investigation and corrective action report. The report states that "the Deviations [for the out of specification balances] fall below the **[redacted]** set out in CAPS **[redacted]**" However, there is no reference to a **[redacted]** acceptance criterion in CAPS standard operating procedure **[redacted]**. Please explain this discrepancy between your completed investigation and corrective action report and standard operating procedure **[redacted]**. Also, please provide a thorough account of the events that led to the deviations, discuss whether there was any product impact, and support your conclusions that the deviations were within normal compounding practices and that they were not clinically significant.

- Failure to have an adequate Quality Assurance (QA) program in place that ensures that your drug preparation activities and processes are monitored, evaluated, corrected and improved. (This observation was noted during the inspections of CAPS facilities in Lanham, MD, Homewood, AL, Horsham, PA, and Kansas City, MO.)

During the inspections, we noted that CAPS QA organization failed to assure that critical activities were performed during the preparation of sterile drugs. For example, your written procedures require that each environmental monitoring sample that tests **[redacted]** be sent to your **[redacted]** for **[redacted]** each **[redacted]**. Your QA program, however, failed to assure that this activity was performed for the 2nd quarter of 2005 at CAPS Lanham, MD, facility. Additionally, activities such as environmental monitoring, personnel training, and equipment calibration and maintenance have not been routinely performed. These deficiencies, as well as the objectionable practices observed at your facilities described above, and the independent confirmation, (by the CDC, the FDA, and **[redacted]** of microbial contamination in intact units of your **[redacted]** solutions, are further indications that your current Quality Assurance program is unable to assure the quality of your sterile preparations.

Your November 25, 2005 and December 12, 2005, responses state that you have identified one CAPS employee per facility who will be assigned to the "temporary, integrated production/Quality Control Unit (QCU), and will perform quality assurance duties until the corporate wide reorganization of the CAPS QA Department has been completed." We are concerned that this interim QCU employee, who performs his o her normal production duties in addition to the new QCU responsibilities, will not be effective in enforcing your firm's practices and procedures. CAPS' written procedures do not specify the roles and responsibilities of the temporary, integrated production/QCU personnel. Furthermore, CAPS current qualit assurance philosophy (CAPS **[redacted]**, which was in place prior to the close of the facility inspections, require the active participation of those individuals most likely to observe quality improvement opportunities.CAPS interim QCU unit approach is identical to your firm's **[redacted]** approach, in that both assign the same production and QCU dual role to certain CAPS employees. Based on the inspectional findings, the **[redacted]** approach has been unable to provide assurance that the activities critical to sterile compounding are consistently performed. Please explain more specifically how the "temporary, integrated production/QCU" will succeed in assuring that the critical sterile compounding activities will be consistently performed.

Additionally, your November 25, 2005, response states that CAPS is currently implementing a corporate

wide reorganization of the QA Department, where an independent QCU will be identified at each CAPS facility, and will report directly to the CAPS QA Regional Manager. In reviewing CAPS procedure, **[redacted]**, we note that the "Pharmacy Staff" is responsible for specific Quality Assurance functions suc - **[redacted]** of **[redacted]** of **[redacted]** and monitoring **[redacted]** and **[redacted]** record review d **[redacted]**. However, the Quality Control Unit for each pharmacy does not share any of these responsibilities with the "pharmacy staff." Instead, QCU's responsibilities consist of **[redacted]** and reporting incidents, coordinating **[redacted]** review meetings, **[redacted]** and **[redacted]** and **[redacted]** with SOPs, testing and "Quality Indicators." Furthermore, upon reviewing the proposed CAPS reorganization chart, we have noticed the "QA Department" and the "onsite QCUs" are under the **[redacted]**, while production personnel separately report to the **[redacted]**." This system does not appear adequate to address the problems with your current quality control process. Please clarify how the QCU will monitor, evaluate, correct, and improve CAPS pharmacy compounding activities and processes if they do not have responsibility for the critical quality assurance activities related to pharmacy compounding, and are essentially excluded in **[redacted]**.

E. Misbranded [redacted] Solutions

Your contaminated **[redacted]**solutions are misbranded within the meaning of Section 502(a) of the Act (21 U.S.C. § 352(a)) because their labeling is false and misleading. Additionally, these products are misbranded within the meaning of Section 502(j) of the Act (21 U.S.C. § 352(j)) because they are dangerous to health when used in the manner suggested by their labeling. The labeling designates these products as **[redacted]** solutions. **[Redacted]** solutions are generally used during **[redacted]**. In addition, products used during **[redacted]** are purported to be sterile. As noted above, FDA laboratory testing found that several lots of **[redacted]** solutions, produced by CAPS at the facility in Lanham, MD, were contaminated with several different species of **[redacted]**. The products' labeling is false and misleading because these solutions were not in fact sterile for their intended use. In addition, these products are dangerous to health when used for **[redacted]** because of this lack of sterility. Thus, the contaminated **[redacted]** solutions are misbranded under Sections 502(a) and 502(j) of the Act.

F. Unapproved and Misbranded Drugs [redacted]

PS produces and distributes the **[redacted]** for further manipulation by hospital pharmacies. The **[redacted]** compounded by CAPS at the Santa Fe Springs, CA, facility, and supplied in **[redacted]** containers, is essentially a copy of an FDA-approved **[redacted]** product, Both products are used as sclerosing agents in the treatment of **[redacted]**. As stated in the CPG, typically FDA will not exercise its enforcement discretion for compounded drugs that are copies, or essentially copies, of FDA-approved, commercially available drugs. We understand that CAPS believes that the product's **[redacted]** distinguishes it from the FDA-approved product. Even if this is a sufficient basis to differentiate this **[redacted]** from the commercially available product, it is not produced for specific patients and there does not appear to be a documented medical need for the particular formulation used to produce CAPS **[redacted]** for the patients to whom it is dispensed.

The **[redacted]** products prepared by CAPS at the facility in Santa Fe Springs, CA, are drugs within the meaning of section 201(g)(1) of the Act (21 U.S.C. § 321(g)(1)). They are new drugs under section 201(p) of the Act (21 U.S.C. § 321 (p)), because they are not generally recognized by qualified experts, as safe and effective for their labeled uses. Neither CAPS nor B. Braun have an approved application pursuant to section 505 of the Act (21 U.S.C. § 355) with respect to these products. Accordingly, their introduction or delivery for introduction into interstate commerce violates section 505(a) of the Act (21 U.S.C. § 355(a)).

The **[redacted]** products prepared by CAPS at the facility in Santa Fe Springs, CA, are also misbranded under section 502(f)(1) of the Act (21 U.S.C. § 352(f)(1)) in that their labeling fails to bear adequate directions for their use. Further, these products are not exempt from this requirement under 21 CFR § 201.115, because they are new drugs within the meaning of section 201(p) of the Act (21 U.S.C. § 321(p)) and they lack approved applications filed pursuant to section 505 of the Act (21U.S.C. § 355).

We acknowledge the corrections made by your firm in response to the Form FDA 483 issued at the close of the November 2004 inspection. However, these corrections do not address all of the violations discussed above.

G. Conclusion

Neither this letter nor the observations noted on the Form FDA 483 are intended to be an all-inclusive list of the deficiencies that may exist at your facilities. It is your responsibility to ensure that your operations are in full compliance with all applicable requirements of the Act and the implementing regulations. Federal agencies are advised of the issuance of all warning letters about drugs so that they may take this

information into account when considering the award of contracts.

You should take prompt action to correct these violations, and you should establish procedures whereby such violations do not recur. Failure to do so may result in regulatory action without further notice, :luding seizure and/or injunction.

We request that you reply in writing within 15 working days of receipt of this letter, stating the action tha you will take to correct the noted violations and ensure that corrections will also be put in place at other CAPS facilities that conduct similar prescription drug compounding and distribution activities. If corrective actions cannot be completed within 15 working days, state the reason for the delay and the time within which corrections will be completed.

Your response should be directed to: James C. Illuminati, Compliance Officer, Philadelphia District Office, RM904 HFR-CE140, U.S. Custom House, Room 900, 200 Chestnut Street, Philadelphia, PA, 19106-2973

Sincerely ,

/S/

Thomas D. Gardine
Director, Philadelphia District Office
Office of Regulatory Affairs
Food and Drug Administration

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1 As you may be aware, Section 127 of the FDA Modernization Act of 1997 amended, the Act by adding section 503A, which specified certain conditions under which compounded human drugs could be exempt from particular requirements of the Act. In April 2002, however, the United States Supreme Court struck down the commercial speech restrictions in section 503A of the Act as unconstitutional . See -Thompson *v Westem States Med. Ctr., 535 U.S. 357 (2002)*. Accordingly, all of section 503A'is now invalid. As a result the agency utilizes its longstanding policy of exercising its enforcement discretion with respect to traditional pharmacy compounding as articulated in Compliance Policy Guide, section 460.200 ("the CPG"), issued on June 7, 2002.

Deaths spur debate about drugs made in pharmacies

Updated 8/7/2006 11:41 PM ET

Enlarge Family handout

Albert Perreault, right, died in March 2004 after undergoing heart surgery at Mary Washington Hospital. His widow, Sue Carol Perreault, left, is suing the hospital and the pharmacy that made the unsterile drugs he was given during surgery.

STERILE STANDARDS

The following states have adopted sterile compounding standards:

Arkansas
Indiana
Louisiana
Massachusetts
Missouri
New Mexico
Ohio
Texas
Utah
Virginia
West Virginia
South Carolina

Source: USP and USA TODAY research

By Julie Appleby, USA TODAY

In eight days last summer, the same dangerous inflammation struck three cardiac surgery patients at Mary Washington Hospital within hours of their operations. On Sept. 2, one man died.

The unusual cluster of cases alarmed chief cardiac surgeon John Armitage, who feared a contaminant was in the surgery center. Tests confirmed it: Bacteria were found in a solution injected into patients' hearts during surgery.

The Fredericksburg, Va., hospital shut down its cardiac surgery program the next day and called state health officials, who brought in the Food and Drug Administration and the Centers for Disease Control and Prevention. Within days, the FDA and the CDC confirmed the presence of several types of bacteria in opened and unopened bags of the cardiac surgery solution, a state report later showed.

The hospital later determined that at least 11 cardiac surgery patients were stricken during a 10-month period from the end of December 2004 to September 2005, and three died. The illnesses and deaths drew attention to a practice few patients know about: Some drugs, including high-risk sterile preparations, are made in pharmacies under less-restrictive rules than those that drug companies follow.

LAWSUITS : Families blame contamination for 4 deaths

The troubles at Mary Washington raise questions about the oversight of such pharmacies by hospitals, state regulators and the FDA. Almost all hospital pharmacies do some type of drug making, called compounding, ranging from low-risk procedures, such as adding medications to intravenous solutions, to high-risk work, such as making sterile treatments from scratch.

In most states, hospitals are not required to test the sterility or potency of products made in their own pharmacies or purchased from outside pharmacies. The frequency and thoroughness of state inspections of the pharmacies vary widely, and the FDA's role in oversight is sometimes hampered by questions over whether it has jurisdiction over what generally is a state matter.

Scrutiny of the pharmacy that served Mary Washington and 45 other mid-Atlantic medical facilities set off a cascade of actions: Virginia health officials pegged the contaminated solution as the likely culprit in the cluster of patient illnesses. All injectable medications made by the pharmacy during a six-week period were recalled, the pharmacy lost its Maryland license temporarily, and its parent company received an eight-page letter from the FDA outlining problems in five of its facilities nationwide.

The hospital was cleared to reopen its surgery program two weeks after the testing. The pharmacy, owned by one of the nation's largest such firms, regained its state license in January. But Armitage is still troubled by what he's learned about the oversight of drug-making pharmacies.

"Whose responsibility is it to regulate these companies that are providing products to essentially every major hospital in the country?" Armitage says. "I just don't see how it can be left to the states alone."

Updating rules

Most hospitals in the USA are involved in making drugs, generally because some of the products they need aren't made by commercial drug companies or patients need specific mixtures. Compounded treatments can include chemotherapy drugs, liquid feeding solutions and intravenous solutions.

Before the rise of large drug companies, most prescriptions were made in pharmacies. Now, the National Association of Boards of Pharmacy estimates that pharmacy-made compounds account for 1% to 5% of all prescriptions.

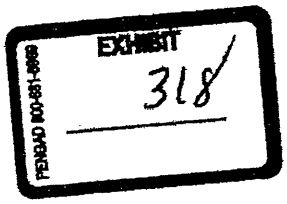
Time pressure, or the cost of having the staff and equipment to mix drugs, leads some hospitals to hire outside pharmacies to make compounded products, including difficult-to-prepare sterile drugs.

In 2003, Mary Washington hired Central Admixture Pharmacy Services (CAPS) in Lanham, Md., to produce a blended cardiac surgery drug called cardioplegia, the hospital says. The solution stops the heart from beating during bypass surgery and must be sterile because it is infused directly into the heart.

CAPS, owned by B. Braun Medical, has 20 locations across the country and supplies 400 medical facilities, according to its website. Its pharmacies make a variety of treatments, including those used to induce labor and treat dialysis patients.

Because of its size, it is one of a few pharmacies that fall under regular FDA oversight, with routine inspections scheduled about every two years. Most pharmacies, even those that make sterile products, are smaller and are overseen by state inspectors, not the FDA.

Rules governing such pharmacies vary by state.



In Maryland, where CAPS has one pharmacy, regulators are updating rules governing preparation of sterile drugs in pharmacies, says John Balch, president of the Maryland Board of Pharmacy.

Despite efforts to beef up oversight of sterile-drug making by pharmacies, only 12 states have adopted new standards set in 2004 by U.S. Pharmacopeia, a non-profit drug-safety organization. Some hospitals have updated their pharmacies to meet the standards, which can mean buying expensive equipment, but many others have not. "This affects most hospitals," says Dale Woodin of the American Society for Health Care Engineering. "All of this is a balance. We're trying to meet patient needs and balance resources."

The standards, a detailed set of rules governing everything from staff training to how to set up a "clean room" to produce sterile drugs, were created partly in response to two separate incidents a few years earlier, when contaminated, pharmacy-made medicines killed three people in California and one in South Carolina.

Revamped rules

Nevada also is revamping its rules. Pharmacy board attorney Louis Ling says the new rules will require any pharmacy making compounded batches of drugs to test them for sterility and potency. Special "clean rooms" and equipment will be required, and employees will have to don protective clothing to make sterile drugs.

"It's going to change everyone's practices," says Ling. "Some (pharmacies) are really close, and some are very good. But nobody in Nevada is fully compliant."

CAPS' website advertises that it meets the new standards, and the company runs programs that teach other pharmacies how to comply with the rules.

But FDA investigators found some of CAPS' facilities falling short of good manufacturing practices.

In March, the FDA sent a letter to B. Braun, CAPS' parent company, outlining problems in five facilities nationwide, including the one in Maryland. Problems ranged from a lack of training in sterile techniques to failing to monitor environmental conditions inside the pharmacies. One Kansas City worker was seen smoking a cigarette outside in his clean-room gown, then, without changing his gown, going back into the area where sterile preparations are made. The firm also failed to confirm that its equipment was properly calibrated.

Tests the FDA ran on unopened bags of the solution CAPS made for Mary Washington late last summer found several types of bacteria, according to a report from the Virginia Department of Health.

"Contaminated cardioplegia solution ... was determined to be the most likely source of the cluster of systemic inflammatory response syndrome" (SIRS) cases at Mary Washington, the health department report says. Another report, from the Maryland pharmacy board, confirms that tests found bacteria but "makes no finding of fact" on any relationship between the contaminated solution and the cluster of injuries and deaths.

The hospital says it is not to blame for the illnesses and deaths.

"With all the information we've received from the department of health, the FDA and our own investigation, we still firmly believe that the severe SIRS cluster in a small number of surgery patients was due to contaminated cardioplegia (solution) and not any fault of the hospital," says Kathleen Allenbaugh, spokeswoman for the 412-bed hospital.

In a written statement provided to USA TODAY, CAPS said it does not have sufficient information to comment on the findings in the Virginia Health Department report. "Before any conclusion can be made in this matter, a review of the entire chain of events, including the handling, storage and administration of the cardioplegia solutions must be completed," the company said. It added that patient safety is its highest priority.

"It has not been determined that any CAPS Lanham products contributed to the tragedy at Mary Washington Hospital," the statement said. "Immediately upon hearing about the issue at this hospital, we voluntarily recalled all types of unused product."

In its statement, CAPS said all its pharmacies are compliant with the new standards and are inspected regularly by the FDA. The company is not currently making cardioplegia solution at Lanham, but it is supplying customers from other facilities, the statement said.

This spring, eight families filed a lawsuit against CAPS and Mary Washington, seeking damages for injuries and deaths they allege resulted from the use of contaminated cardiac solution.

Making safe products

Pharmacists say their products are safe, are requested by doctors for individual patients because no other option exists commercially and are made following sterile-drug-preparation standards.

The International Academy of Compounding Pharmacists, which declined an interview, said in a statement that it supports the 2004 sterile standards and endorses a model set of regulations put forward by the National Association of Boards of Pharmacy.

Critics such as Sarah Sellers, a consulting pharmacist who served on an FDA advisory board on compounding until 2002, say that the standards for sterile-drug preparation are rarely enforced and that some high-risk sterile products should not be made in pharmacies at all. Updating pharmacies to meet the new standards required by some states often involves installing new equipment, such as ventilation systems and clean rooms.

The American Hospital Association says estimates to update facilities range from $50,000 to $1.5 million. The range reflects that some hospitals have already done quite a bit to upgrade facilities, while others may need much work.

Some hospitals and pharmacies have balked at spending money to update, says Eric Kastango of Clinical IQ, a health care consulting company that works with clients that need assistance in sterile compounding and quality systems. "If they're going to do compounding, they have to do it correctly and make the investment," he says.

Higher risks?

Some say the risks when smaller, less-sophisticated hospitals do much of their own sterile compounding may be higher than when outsourcing such work to vendors such as CAPS.

"Sterility is an area that we're very concerned about," says Steve Silverman, acting assistant director at an FDA compliance office. "So we closely monitor firms like CAPS, which train their personnel and have procedures designed to minimize risk. If these firms were to disappear, then sterile compounding likely would return to hospital and local pharmacies that may be less-well-equipped."

Armitage at Mary Washington says he hopes some good comes out of the troubles. New standards would help, he says. Hospitals, he says, should test products they buy from outside vendors for sterility. He and spokeswoman Allenbaugh say that better communication between the FDA and hospitals would help. Hospital officials had to use the Freedom of Information Act to find out what the FDA uncovered in its inspections of CAPS facilities.

Since reinstatement of Mary Washington's heart program, there have not been any unusual clusters of the inflammatory syndrome, Allenbaugh says.

The hospital now makes its own cardioplegia solution. Says Armitage: "What we don't use that day, we throw away."

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FDA Consumer Health Information

Photofest

The Special Risks of Pharmacy Compounding

Pharmacy compounding is an age-old practice in which pharmacists combine, mix, or alter ingredients to create unique medications that meet specific needs of individual patients.

It's also a practice that is under FDA scrutiny—mainly because of instances where compounded drugs have endangered public health.

"In its traditional form, pharmacy compounding is a vital service that helps many people, including those who are allergic to inactive ingredients in FDA-approved medicines, and others who need medications that are not available commercially," says Kathleen Anderson, Pharm.D, Deputy Director of the Division of New Drugs and Labeling Compliance in FDA's Center for Drug Evaluation and Research (CDER).

Compounded medications are also prescribed for children who may be unable to swallow pills, need diluted dosages of a drug made for adults, or are simply unwilling to take bad-tasting medicine.

"But consumers need to be aware that compounded drugs are not FDA-approved," Anderson says. "This means that FDA has not verified their safety and effectiveness."

Steve Silverman, Assistant Director of CDER's Office of Compliance, says that poor practices on the part of drug compounders can result in contamination or in products that don't possess the strength, quality, and purity required. "And because patients who use these drugs may have serious underlying health conditions," he says, "these flawed methods pose special risks."

Unlike commercial drug manufacturers, pharmacies aren't required to report adverse events associated with compounded drugs. "FDA learns of these through voluntary reporting, the media, and other sources," says Silverman.

The Agency knows of more than 200 adverse events involving 71 compounded products since 1990. Some of these instances had devastating repercussions.

- Three patients died of infections stemming from contaminated compounded solutions that are used to paralyze the heart during open-heart surgery. FDA issued a warning letter in March 2006 to the firm that compounded the solutions.
- Two patients at a Washington, D.C., Veterans Affairs hospital were blinded, and several others had their eyesight damaged, by a compounded product used in cataract surgery. The product was contaminated with bacteria. In August 2005, FDA announced a nationwide recall of this Trypan Blue Ophthalmic Solution. Contaminated solution had been

distributed to hospitals and clinics in eight states.

- In March 2005, FDA issued a nationwide alert concerning a contaminated, compounded magnesium sulfate solution that caused five cases of bacterial infections in a New Jersey hospital. A South Dakota patient treated with the product developed sepsis and died.

A Troubling Trend

The emergence over the past decade of firms with pharmacy licenses making and distributing unapproved new drugs in a way that's clearly outside the bounds of traditional pharmacy is of great concern to FDA.

"The methods of these companies seem far more consistent with those of drug manufacturers than with those of retail pharmacies," says Silverman. "Some firms make large amounts of compounded drugs that are copies or near copies of FDA-approved, commercially available drugs. Other firms sell to physicians and patients with whom they have only a remote professional relationship."

FDA highlighted these concerns in August 2006, when it warned three firms to stop manufacturing and distributing thousands of doses of compounded, unapproved inhalation drugs nationwide.

Inhalation drugs are used to treat diseases including asthma, emphysema, bronchitis, and cystic fibrosis. "These are potentially life-threatening conditions for which numerous FDA-approved drugs are available," says Silverman. "Compounded inhalation drugs may be distributed to patients in multiple states, and patients and their doctors may not understand that they are receiving compounded products."

Enforcement

"FDA historically hasn't directed enforcement against pharmacies engaged in traditional compounding," says Anderson. "Rather, we've focused on establishments whose activities raise the kinds of concerns normally associated with a drug manufacturer and whose compounding practices result in significant violations of the new-drug, adulteration, or misbranding provisions of the Federal Food, Drug, and Cosmetic Act."

FDA counts compounded drugs among the new drugs that are covered under the Act. "We consider them new because they're not generally recognized among experts as safe and effective," says Anderson.

She adds that FDA recognizes that states have a central role in regulating pharmacy compounding. "We refer complaints to the states, support them when they request it, and cooperate in investigations and follow-up actions. But there are cases when states are unable to act, and we proceed without them," Anderson says.

Red Flags

In a May 29, 2002, Compliance Policy Guide devoted to human pharmacy compounding, FDA identifies factors that it considers in deciding upon enforcement action. These factors include instances where pharmacists are:

- compounding drug products that have been pulled from the market because they were found to be unsafe or ineffective.
- compounding drugs that are essentially copies of a commercially available drug product.
- compounding drugs in advance of receiving prescriptions, except in very limited quantities relating to the amounts of drugs previously compounded based on valid prescriptions.
- compounding finished drugs from bulk active ingredients that aren't components of FDA-approved drugs, without an FDA-sanctioned, investigational new-drug application.
- receiving, storing, or using drug substances without first obtaining written assurance from the supplier that each lot of the drug substance has been made in an FDA-registered facility.
- failing to conform to applicable state law regulating the practice of pharmacy.

What You Can Do

What can consumers do to protect themselves against inappropriate drug-compounding practices? Ilisa Bernstein, Pharm.D, J.D., Director of Pharmacy Affairs in FDA's Office of the Commissioner, offers these tips:

- Ask your doctor if an FDA-approved drug is available and appropriate for your treatment.
- Check with the pharmacist to see if he or she is familiar with compounding the product in your prescription.
- Get information from your doctor or pharmacist about proper use and storage of the compounded product.
- If you receive a compounded product, ask the pharmacist if the doctor asked for it to be compounded.
- If you experience any problems or adverse events, contact your doctor or pharmacist immediately and stop using the product.
- Report any adverse events experienced while using the product to FDA's MedWatch program at *http://www.fda.gov/medwatch/* FDA

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Pharmacy Compounding Primer for Physicians

Prescriber Beware

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Abstract

Go to:

Since the development of federal standards for drug approval, the practice of medicine has historically involved the compounding of medications based on a physician's determination that a US FDA-approved product either did not exist, or could not be used for medical reasons. Today, prescriptions for non-FDA-approved compounded drugs may be driven by fanciful and largely unregulated pharmacy advertisements to physicians and patients and/or payer reimbursement policies, thus placing prescribers in the backseat for clinical decision making. This article outlines essential differences between FDA-approved drugs and compounded drugs and reasserts the primary medical role of physicians for determining what medical circumstances may necessitate treatment with non-FDA-approved products. In addition, liability concerns when prescribing non-FDA-approved drugs are discussed. While representing a US perspective, underlying principles apply globally in the setting of magistral and extemporaneous formulations produced outside national regulatory frameworks.

1. Introduction

Go to:

Since the development of federal standards for drug approval, the professions of pharmacy and medicine have their earliest roots in drug compounding. In centuries past, doctors and pharmacists created individual therapies according to patient needs and the medical and scientific principles of the time. With the development of commercial manufacturing, pharmacies gradually transitioned into dispensaries of standardized drug products manufactured by the pharmaceutical industry and subject to federal oversight and regulation. While US FDA-approved drug products currently meet the therapeutic needs of most patients, there are certain circumstances in which compounded drugs play an important role in medical care. While the scope of the paper is focused primarily on the US experience, principles apply equally to magistral or extemporaneous formulations that are produced outside national regulatory frameworks around the globe and for which differentiation and discrimination of this unique benefit-risk setting is critical for therapeutic decision making.

2. Drugs Approved and Regulated by the US FDA

Go to:

FDA-approved drugs include both branded and generic products. Branded drugs are rigorously reviewed by the FDA for quality, safety and efficacy under a New Drug Application (NDA). Approval of an NDA requires substantial evidence of effectiveness, defined under the Federal Food, Drug and Cosmetic Act (FFDCA) as "evidence consisting of adequate and well-controlled investigations by experts qualified by scientific training and

experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling."[1] In general, drugs approved under an NDA have demonstrated a positive benefit-risk balance for their intended use on a population level. Generic drugs are reviewed and approved for quality and bioequivalency to an FDA-approved reference drug under an Abbreviated NDA (ANDA). Both brand and generic drugs are required by law to be produced under federal Good Manufacturing Practice (GMP) regulations, a detailed and complex set of working standards established through federal regulation to ensure products meet specific requirements for identity, quality, potency and purity. Pharmaceutical manufacturers are periodically inspected by the FDA for adherence to GMP regulations and to ensure that GMP-driven quality standards established for drugs manufactured for scientific evaluation in clinical trial populations[2] are met or exceeded for drugs manufactured for commercial distribution.[3]

3. Compounded Drugs and Traditional Pharmacy Compounding

Go to:

In response to a prescription, pharmacists may combine, mix or alter ingredients to create unique medications in accordance with traditional compounding. A compounded drug may be necessary, for example, to treat a patient with a documented allergy to a drug ingredient, or to provide a liquid dosage form for a child who is unable to swallow tablets. A primary tenet of traditional compounding is that an FDA-approved product should be used wherever possible to meet a patient's individual medical needs, because, despite best compounding practices,[4] extemporaneous formulations generally lack studies to document stability, bioavailability, pharmacokinetics, pharmacodynamics, efficacy and safety.[5,6] This tenet restricts the use of compounded drugs to where they are medically necessary and protects the public from intentional circumvention of the FDA approval and regulatory process that consumers rely on for safe and effective therapies (table I).

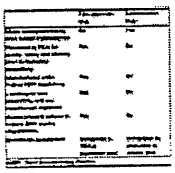

Table I

Key differences between US FDA-approved and compounded drugs

State Boards of Pharmacy oversee pharmacy practices, including drug compounding. When the FDA learns of compounding practices that raise public health concerns, the agency may refer the matter to State Boards of Pharmacy for investigation.[7] Using a risk-based approach,[8] the FDA may take enforcement action against pharmacies for circumstances described in FDA Guidance that are not consistent with traditional compounding, including but not limited to the following:[9]

1. Compounding drugs prior to receipt of a valid prescription.
2. Compounding drugs removed from the market for safety reasons.
3. Compounding drugs that are essentially copies of commercially available products.

Compounded drugs may be made starting with FDA-approved brand or generic drugs, for example, a tablet or capsule may be converted to a liquid form for administration to a child. Benefits of compounding from approved dosage forms include basic confirmation of the identity of the active ingredient and its initial dose. Potential disadvantages include formulation complications from inactive ingredients that may not be suitable for the compounded formulation.

Compounded drugs may also be made with active pharmaceutical ingredients (API) and other inactive components. Benefits of compounding from APIs include the avoidance of binders, and the possibility of accessing drug substances that are not available in suitable commercial forms for the intended use of the compounded product. For example, an oral tablet may contain inactive ingredients that should not be administered

by the intravenous route. If such a drug is necessary, it may be preferable to start with an appropriate API, if available. Disadvantages of compounding with APIs include, first and foremost, uncertainty regarding the substance's identity, purity and potency. In addition, due to the complex nature of our global supply chain, an API's origin and disposition throughout the supply chain, including shipping, storage conditions and repackaging, may be difficult for pharmacies and physicians to verify.[10]

By necessity, compounded drugs are made under standards that are less stringent than those applied to FDA-approved products. It would be impossible, for example, to apply for FDA approval for drugs compounded on an individual, extemporaneous basis. Further, traditional pharmacies would find it difficult to comply with the complexities of federal GMP requirements under the FFDCA. However, some facilities operating under less rigorous pharmacy standards actually manufacture large quantities of standardized dosage forms without adherence to federal manufacturing standards. Such business practices, deemed by former FDA Commissioner David Kessler, MD, as "manufacturing under the guise of pharmacy compounding," undermine the FFDCA and place populations at risk for substandard drug exposures.[11] Because of the inherent differences between federal manufacturing and approval standards and professional (pharmacy) standards with respect to purpose, scope and enforceability, physicians should be cautious in their judgements regarding what circumstances would justify setting aside a federal standard for a professional one.

3.1 Risks Associated with Compounded Medications

Pharmacy-compounded drugs have been associated with quality defects, infectious disease outbreaks and other adverse events which, in some cases, have involved patient deaths.[7,12–17] Because federal surveillance requirements do not exist for compounded drugs, the extent of quality and safety problems is unknown.[18]

3.1.1 Substandard Products While surveillance is limited, quality defects have been reported in conjunction with product recalls, as outcomes of formal, limited investigations by the FDA and Missouri State Board of Pharmacy, and as independent studies.[17,19–24]

In 2004, roughly 1.4 million doses of compounded respiratory solution contaminated with *Burkholderia cepacia* were distributed to patients nationally. The Missouri State Board of Pharmacy found the pharmacy did not adequately recall potentially affected product and failed to advise patients and prescribers of the contamination risk. The Board issued a temporary restraining order, noting in their petition that the pharmacy "engaged in practices that pose a threat of immediate and irreparable injury, loss or damage to patients and presents a probability of serious danger to the health, safety or welfare of the residents of the state."[25]

In 2006, the FDA conducted a limited survey of compounded drugs. Of 36 samples tested by the FDA, 12 failed at least one quality test, for a failure rate of 33%. Further, oral hormone dosage forms containing multiple active ingredients showed poor content uniformity, with random variation in all three active ingredients from capsule to capsule.[19]

The Missouri State Board of Pharmacy initiated routine sampling and testing of compounded drugs after pharmacist Robert Courtney was found to have supplied thousands of cancer patients with substandard chemotherapy that provided only a fraction of prescribed doses.[26] For the years 2006–2009, the Board of Pharmacy testing revealed that failure rates averaged roughly 20% (range 11.6–25.2), with individual findings ranging from 0% to 450% of labelled potency.[23] While the Courtney case involved drug reconstitution and admixing of FDA-approved products, it is critical to this discussion because it illustrates an important limitation of clinical medicine: the dilution scheme went on for years and affected thousands of patients, yet medical observation alone failed to detect lack of effect, including both therapeutic response and expected chemotherapy-related toxicity. In the absence of federal oversight, clinical observation or experience alone may be a poor surrogate for ensuring the quality, safety and effectiveness of compounded drugs.

In a 2004 published analysis sponsored by STD Pharmaceuticals,[27] all samples purchased from three compounding pharmacies failed content testing for a 3% sodium tetradecyl sulfate solution for injection (range

2.59–3.39). Significant concentrations of the contaminant carbitol were found to be present in samples from all three sources (0.33–4.18), suggesting possible use of a non-pharmaceutical grade chemical. In response to the assay results, dermatologist Mitchel Goldman concluded that "Physicians need to be aware that the stated concentration may not be correct and that along with sodium tetradecyl sulfate, potentially harmful contaminants may be present in the solution."

Mahaguna et al.[28] reported an analysis of compounded progesterone suppositories from ten randomly selected pharmacies. Nine of the ten pharmacies provided suppositories that fell outside potency limits set for approved products and one pharmacy provided suppositories testing positive for *Comamonas acidovorans* bacteria.

In a similar analysis sponsored by Ther-Rx Corporation, eight of nine samples of hydroxyprogesterone caproate API accessible to pharmacies for compounding did not meet impurity standards applicable for manufacturing the approved product and 16 of 30 samples of hydroxyprogesterone injection samples purchased from compounding pharmacies exceeded impurity limits for the approved product. One additional sample of API labelled as hydroxyprogesterone caproate did not contain any active ingredient and was subsequently found to contain only glucose.[17]

3.1.2 Morbidity and Mortality Associated with Compounded Drugs Because pharmacies are not required to conduct surveillance or report adverse events associated with drugs they make, the extent of compounded drug-associated morbidity and mortality cannot be assessed. Sentinel events involving compounded drugs have become known through sporadic reporting by the FDA and the Centers for Disease Control and Prevention (CDC), through case reports published in the literature, and through media reporting. These events are considered the 'tip of the iceberg' by public health experts, because there is little if any transparency as to the extent of exposure to non-FDA-approved, pharmacy compounded drugs and the rate of occurrence of adverse events.[12]

Examples of preventable adverse events include but are not limited to the following:

- An outbreak of *Pseudomonas fluorescens* bloodstream infections associated with compounded catheter flush solutions occurred in four states during 2004–5. The CDC noted that sterility testing of finished products, mandated for FDA-approved products, was reportedly not performed in this case and concluded "Companies that manufacture products intended for injection should follow FDA regulations for ensuring the sterility of these products."[14]
- Whelan et al.[15] reported a probable treatment failure in a poorly controlled asthma patient with severe disease. An analysis found that the patient's inhalation therapy contained an average of 36.8% of active ingredient for the five vials assayed by high-performance liquid chromatography (HPLC). Authors note that these findings highlight major concerns with using compounded products that are not FDA approved.
- A cluster of streptococcal endophthalmitis infections was reported to the FDA by the Florida Department of Health following intravitreal injection of repackaged bevacizumab (Avastin®). At least 12 patients developed eye infections, with some losing all remaining vision.[16]

3.2 Controversial Roles of Compounding

While there is a place for traditional pharmacy compounding to fulfil medical needs of individuals that cannot be met with commercially available products, these more controversial aspects threaten to circumvent important public health regulations at the population level. Some controversial uses of pharmacy compounding include the introduction of drug moieties that have been denied or removed from the US market, the mass marketing of specific, non-FDA-approved formulations, and the compounding of drugs for economic reasons.

An interesting example involves the drug 4-aminopyridine. Although physicians had been prescribing unapproved versions of the drug for up to 20 years, it was not until the drug was studied systematically that rare seizures were discovered as a potential side effect. In this case, the medical profession pushed for an approved version to be marketed, rationalizing that if a seizure occurred in the context of a patient taking an FDA-approved alternative,

"at least you know it wasn't because of a local compounding pharmacy error."[29]

Another significant example has been the rapid growth of the so-called 'bioidentical postmenopausal hormone therapy' market. Following the abrupt termination of the estrogen-progestogen arm of the National Institutes of Health (NIH) Women's Health Initiative Study in July 2002, an alternative market developed promoted by compounding pharmacies and health providers, often with cross-interests. Not subject to the reporting requirements imposed on the pharmaceutical industry, the bioidentical compounding industry has made major claims of absence of risk and maintenance of benefits of hormone therapy, despite the fact that the basic molecules being compounded are, in most instances, the same as those of FDA-approved products.[30] The FDA has found discrepancies and has issued Warning Letters to many compounders, but this alternate industry continues to flourish with major marketing efforts.[31]

An example of pharmacy compounding purely for cost-saving purposes involves the recently approved drug, Makena® (17α-hydroxyprogesterone caproate injection). Citing a "unique circumstance," the FDA announced the agency would continue to exercise enforcement discretion and not enforce the FFDCA for compounded versions of the newly approved drug if pharmacies produced the alternatives in accordance with "traditional compounding."[32] The announcement created considerable confusion in the prescribing and reimbursement communities, to the extent that some stakeholders interpreted the FDA enforcement discretion language to mean that compounded versions of 17α-hydroxyprogesterone caproate had been approved by the FDA for safety and efficacy. On 29 June 2012, the FDA clarified its regulatory language for prescribers, payers and patients, stating that "when an FDA-approved drug is commercially available, the FDA recommends that practitioners prescribe the FDA-approved drug rather than a compounded drug unless the prescribing practitioner has determined that a compounded product is necessary for the particular patient and would provide a significant (medical) difference for the patient as compared to the FDA-approved commercially available drug product."[8] This statement holds at its very core the fundamental public health values of the FFDCA. FDA-approved products produced under federal GMPs represent an essential standard of pharmaceutical care relied on by US citizens, and deviations from this standard of care should be made only under rare circumstances of medical necessity.

3.3 Medico-Legal Risks for Physicians

Few prescribing physicians escape concerns during their day-to-day practice of the 'lawyer looking over their shoulder'. The prescribing of compounded drugs involves the triad of patient, physician prescriber and compounding pharmacy. When prescribing an FDA-approved drug according to labelled indications, in the event of an adverse outcome the physician is protected by tthe FDA approval process and background support of a major pharmaceutical company, thus unlikely to face personal liability. Unlike FDA-approved products, there is no requirement by compounders to provide a patient package insert listing risks and benefits, and the marketing invariably has minimized possibility of risks. Consequently, prescribers of compounded products may be personally exposed should there be an adverse event as a result of administering a product that neither the prescriber nor the compounder can prove to have been pure and free of active contaminants, of correct dose, sterile, etc.[33] Indeed, the FDA has attempted to avoid such risks by its policy against compounding products when an FDA-approved drug exists. Physicians should also be aware that the liability based on inappropriate use of a non-FDA-approved drug can be significant, and possible negative consequences can include the invalidation of their malpractice insurance, personal liability and possible criminal prosecution. This is a situation beyond buyer beware that really is 'prescriber beware'.

Prescribing physicians can lessen malpractice exposure. The simple and direct approach would be to only prescribe FDA-approved products, with the sole exception for those patients who require an alternative form that is not available commercially.[34] If prescribers are motivated to prescribe compounded products, and reduced cost is not legally viable as a sole reason, then that prescriber needs to take some active steps to ensure the patient is receiving exactly what was prescribed. These include ascertaining that an FDA-approved equivalent is not available, acquiring information from the compounding pharmacist as to whether their facility is FDA registered,

where the raw product was obtained and whether it is pharmaceutical grade for humans, how the batch is stored, whether it has been tested for purity, how and when the product was compounded including sterility, and whether the equipment is free of contaminants of other drugs. It is strongly recommended that documentation about responses to these queries be included in the patient record, confirming that the prescriber has taken every step available to them to ensure that the patient is receiving the medication prescribed.

4. Important Considerations for Prescribers

Go to:

Compounding practices have emerged throughout the US and other countries as novel pharmacy business models that offer expanded compounding services with direct marketing of unique formulations to patients and prescribers. Because the idea of using a compounded product in today's marketplace may not arise solely from a physician's identification of a medication problem that requires an alternative to an FDA-approved product, physicians should have a basic understanding of the benefits and risks of compounded drugs to support therapeutic decision making and to help educate patients about their treatment options. In this regard, prescribers are reminded of the following:

- That compounded drugs lack an FDA finding of safety, efficacy and manufacturing quality.
- That compounded drugs are not interchangeable with FDA-approved brand or generic medications.
- That, if an FDA-approved drug is available, the FDA-approved product should be prescribed and used.
- That liability concerns may arise due to prescribers' role as a learned intermediary if patient harm arises in association with compounded drugs.

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Subpotentcy of a Compounded Budesonide for Nebulization Product in a Patient with Poorly Controlled Asthma

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Abstract

RATIONALE: Compounding of nebulized medications for patients may be regarded as a matter of convenience and decreased cost for patients. Use of compounded products are generally discouraged due to concerns of stability and sterility. We recently evaluated a poorly controlled, severe asthmatic who had been on a compounded budesonide preparation for nebulization.

METHODS: HPLC was performed on five of the patient's budesonide nebules (0.5 mg in 2.5 mL), and were compared to a Pulmicort Respule® of the same strength (0.5 mg in 2 mL). Additionally, we attempted to simulate extreme storage conditions by exposing the Pulmicort Respule® to high temperatures (1278 F), and to sunlight, by placing in an automobile for 72 hours.

RESULTS: The average amount from the five patient samples yielded 36.8% (183.8 µg) of the labeled claim (500 µg), whereas the 'control' Pulmicort Respule® produced 91.3% (456.2 µg) of the labeled claim (500 µg). The sunlight exposed sample did not appear to lose potency (93.5%), nor did the heat treated sample (98.7%).

CONCLUSIONS: These findings highlight a major difficulty in using a non-FDA approved generically compounded preparation of a nebulized form of budesonide, when compared to the manufacture's product. The end result was that the patient received a fraction of the prescribed dose, which may have contributed to his poor control. In addition, it is unclear whether this compounded suspension delivered an adequate particle size distribution in the respirable range.

USP <797> GAP ANALYSIS TOOL

[For Compounded Sterile Preparations]

I.V. Insights

Sterile Compounding Consulting

USP<797> Gap Analysis Tool (For Compounded Sterile Preparations)

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Introduction

Over the years, there have been countess examples illustrating how contamination of compounded sterile preparations (CSPs) can cause harm to patients. The U.S. pharmacopeia's (USP) General Chapter <797> *Pharmaceutical Compounding Sterile Preparations* sets forth practice standards meant to help ensure that CSPs are compounded in such a way as to prevent harm to the patients.

The following gap analysis tool is meant to help facilities determine which areas of USP 797 they are in compliance with and which areas they have yet to become compliant with. This tool has taken into account new revisions to USP 797 that became official June 2008 and should be used as a preliminary assessment for compliance with USP 797. One should refer to Chapter 797 for more detail. It should be noted that the following tool has not been provided or endorsed by the USP Convention or the USP Expert Committee on Sterile Compounding. This document is provided for informational purposes only and is not intended as legal advice. It should not be used to replace the advice of your own legal counsel.

To use this tool, follow the 4 steps below. As mentioned above, one should refer to Chapter 797 for more detail if needed. You can also visit our website www.IVInsights.com or contact us at 800-704-2192 for more information or to speak with a consultant.

Definitions

Allergen extracts-refers to subcutaneous injections (single dose or multiple dose) preparations of allergen extracts which are prepared by a physician or designated personnel under a physician's supervision.

BUD-'beyond use date'. The date or time after which a CSP shall not be stored or transported.

BSC-'biological safety cabinet'. A cabinet which has an open front and downward airflow. Air that enters and exits the hood is filter by a HEPA filter to protect compounding personnel and the environment. This type of cabinet is considered appropriate for compounding hazardous preparations.

CAI-'compounding aseptic isolator'. Isolator that maintains an aseptic compounding environment and is made specifically for compounding pharmaceuticals. Air from the area surrounding the isolator must first pass through a HEPA filter before passing into the isolator.

CACI-'compounding aseptic containment isolator'. Isolator specifically designed to protect compounding personnel from airborne drug during the compounding process. Air from the area surrounding the isolator must first pass through a HEPA filter before passing into the isolator. When hazardous drugs are prepared in the CACI, the CACI should be vented to the outside using proper building design. This type of cabinet is considered appropriate for compounding hazardous preparations.

CSP-'compounded sterile preparation'. Compounded preparations that must be sterile when administered to a patient. Includes biologics, diagnostics, drugs, nutrients, radiopharmaceuticals, aqueous bronchial and nasal inhalations, baths and soaks for live organs, injections, irrigations for wounds and body cavities, ophthalmic drops and ointments, and tissue implants

CSTD-'closed system vial transfer device'. This is a device that provides a closed system by which fluids may be transferred without venting hazardous substances into the surrounding environment. Ideal for use when preparing hazardous preparations.

PEC-'Primary engineering control'. A device or room which provides an ISO class 5 environment. Examples include BSC, CAI and CACIs.

Supervisors-for the purpose of this tool, this term refers to supervisors who supervise compounding and/or dispensing activities and are qualified, licensed healthcare professionals

PPE-'personal protective equipment'. Includes gowns, face masks, eye protection, hair covers and shoe covers.

The Process

STEP 1: Define you Risk Level:

Risk Level	**Criteria**
Low Risk Level Compounding of CSPs	• CSPs which only involve the transfer, measuring or mixing of three or less commercially manufactured packages of sterile products. • Compounding of the CSP does not involve more than two entries into any one sterile container.
Low Risk Level Compounding with 12 hour or less BUD	• This applies when the PEC is a CAI or CACI that cannot be located within an ISO 7 buffer area • Only low risk, nonhazardous and radiopharmaceutical CSPs which are patient-specific and made according to a physician's order may be prepared under this classification • Administration occurs within 12 hours of preparation or per manufacturer recommendations, whichever is less.
Medium Risk Level Compounding of CSPs	CSPs are compounded under Low Risk

	Compounding conditions and one or more of the following apply: • More than three sterile products or entries into any container • Sterile products are pooled to make CSPs to be administered to one or multiple patients • Complex aseptic manipulations take place (other than a single volume transfer). • Compounding process is of unusually long duration (i.e. such that requires dissolving ingredients or homogenous mixing). • Compounding of total parenteral nutrition fluids take place using manual or automated devices • Filling of reservoirs of injection/infusion devices which contain three or more sterile drug products and air is evacuated from container prior to dispensing.
High Risk Level Compounding of CSPs	CSPs are compounded and any of the following apply: • Non-sterile ingredients and/or non-sterile devices are used to compound a sterile final product • Commercially manufactured sterile products are exposed to air quality worse than ISO 5 for more than 1 hour. • The CSP lacks effective antimicrobial preservatives and is exposed to air quality worse than ISO 5 for more than 1 hour. • Sterile surfaces of preparation device and/or containers are exposed to air quality worse than ISO 5 or more than 1 hour • Non-sterile water-containing preparations are stored for more than 6 hours before sterilization
Immediate Use CSPs	Immediate use CSPs are exempt from low risk level requirements ONLY when the following apply: • There is an emergent need for immediate administration of a CSP • Examples include 'cardiopulmonary resuscitation, treatment in an emergency room, preparation of diagnostic agents or critical therapy where the preparation of the CSP under conditions described for low risk CSPs subjects the patient to additional

	risk due to delays in therapy. • Does not include preparations that must be stored for future patient use • Medium and high risk CSPs are not to be classified as Immediate Use CSPs. • Immediate use CSPs involve not more than three commercially manufactured sterile, nonhazardous products or radio pharmaceuticals from their original manufacturers' containers with not more than two entries into any one container of sterile solution or administration container/device. • The compounding procedure is continuous and lasts not more than 1 hour • If not immediately administered the CSP is under constant supervision to ensure there is no contact with nonsterile surfaces and/or particulate matter and to prevent mix-ups with other CSPs • Administration of CSP occurs no more than 1 hour after the start of preparation of the CSP • If the CSP is not completely and immediately administered by the person who prepared it (or at least the administration is completely witnessed by the person who prepared it), the CSP bears a label listing the following: patient identification, names and amounts of ingredients, the names and initials of the person who prepared it and the exact 1 hour BUD and time.

STEP 2: Perform Gap Analysis

You may use the tool below to perform a gap analysis of your facility comparing it to the USP 797 standards. This tool is meant to be an instrument and by no means is meant to be used as a comprehensive guide to all of the standards presented in USP 797.

STEP 3: Develop Action Plan

Criteria to which you answered 'no' to will require an action plan. You will have a separate action plan for each criteria you wish to improve upon. If you answered 'yes' to a criteria, but feel you could improve in that area, don't be afraid to utilize an action plan. After all, there is always room for improvement. The action plans you develop should be documented and saved for survey purposes. They

may be used to document to the surveyor that your facility is on its way to compliance with the particular standard. Your surveyor will appreciate your commitment to patient safety and quality.

STEP 4: Implement, adjust and monitor Action Plan

Few action plans will be put into place and never reevaluated for their effectiveness. Most action plans should include a time frame for how often the plan will be revisited and audited. For the purpose of auditing, it helps to write the action plan in such a way that it includes auditable data that is concise and quantitative so that results can be easily assessed at audit time. It is also recommended that thresholds be determined for your facility for each auditable measure that is assessed as part of an action plan. Audit results that exceed the threshold that your facility will require 'tweaking' of the action plan and further follow-up.

Documentation is the key!

It is important to document any and all efforts toward compliance with USP 797. As they say, "If it wasn't documented, it didn't happen." Proper documentation will speak volumes when communicating your compliance efforts to a surveyor.

Gap Analysis Tool

USP 797 Requirements	Yes	No (action required)	Notes
General			
Facility has standard operating procedures which help ensure CSPs are prepared in a quality environment.			
Supervisors who supervise compounding and/or dispensing activities are qualified, licensed healthcare professionals			
Supervisors ensure that staff who engage in compounding are sufficiently skilled and educated. They also ensure that these staff are properly instructed and trained to correctly perform and document compounding and dispensing activities pertaining to: • antiseptic hand cleansing • disinfection of non-sterile			

compounding surfaces • donning of protective garb • maintenance and achievement of ISO Class 5 PEC devices • identification, weighing and measurement of ingredients • manipulation of sterile products aseptically • sterilization of high risk CSPs • label and inspect CSPs for quality			
Supervisors ensure that ingredients are of the correct identity, quantity and purity.			
Partially used and opened ingredient packages for subsequent use in CSPs are stored properly in restricted access areas in the facility. They are not used after the BUD or expiration date.			
Supervisors ensure that devices used to measure, mix, sterilize and purify are clean, accurate and effective.			
Packaging is appropriate to maintain sterility and strength until the BUD of the product.			
Labels of CSPs list names and amount or concentration of each active ingredient.			
Before dispensing a CSP, the following is confirmed: • visual clarity of the CSP • identity and amounts of the ingredients • preparation procedures • sterilization procedures			
Deficiencies in compounding, labeling, quality, packaging and inspection can be rapidly identified and corrected.			
Punctured single-dose containers are used within 1 hour if opened in worse than ISO 5 environment.			
Punctured single-dose containers are used within 6 hour if opened in an ISO 5 environment or better.			
Punctured multiple-dose containers are used within 28 days, or per manufacturer recommendations,			

whichever is less.			
Opened single dose ampuls are not stored for any period of time.			
ISO 7 buffer areas are segregated from surrounding areas and may or may not be physically segregated from the antearea.ISO 7 buffer areas that are physically separated from surrounding areas by doors, walls and pass-throughs maintain a positive pressure of 0.02 to 0.05 inch water column. Buffer areas that are not physically separated from the anteroom exhibit an air velocity of at least 40 ft per minute from the buffer area across the line of demarcation into the ante area.			
Only items (furniture, supplies, equipment) necessary for working within the controlled environment are brought into the buffer area. These items are nonpermeable, cleanable and nonshedding. Items are first cleaned and disinfected before bringing into the buffer area.			
Surfaces in the buffer area are cleanable, smooth, non-shedding and free from cracks. Junctions in the walls and ceilings are caulked or covered.			
Food, drinks and items exposed in patient care areas are not allowed into ante-areas, buffer areas and separate compounding areas.			
Cartons for items needed for compounding (i.e. needles, syringes, tubing sets and drugs) are removed and items are wiped down with sterile 70% IPA (or another disinfectant that does not leave a residue) when possible in an ISO class 8 or better ante-area before entering the buffer area.			
Hand hygiene and garbing is performed in the ante-area. There is some sort of demarcation that separates the buffer area from the ante-area.			
Before entering the segregated			

compounding area or buffer area, personnel remove cosmetics and jewelry. Artificial nails are prohibited while working in the sterile compounding environment.			
Garbing by compounding personnel takes place in the following order: shoe covers, head and facial covers, face masks, eye shields (optional unless working with eye irritants).			
Hand cleansing is performed in the ante area after garbing. First debris is removed from fingernails utilizing a nail cleaner and warm water. Hands and forearms are then washed up to the elbows for at least 30 seconds with soap and water. Lint free disposable towels or electric dryer are used to dry hands and forearms. After this a nonshedding gown with tight fitting wrists and an enclosed neck is donned. Waterless alcohol-based hand scrub is then applied and allowed to dry prior to donning sterile powder-free gloves. Routine disinfection of gloves during compounding with sterile70% IPA occurs whenever nonsterile surfaces are touched. When exiting the compounding area, shoe covers, hair and facial covers, face masks and gloves are removed and replaced before re-entering the compounding environment.			
Cleaning and disinfection procedures are written out in policies and procedures and are followed by personnel.			
Cleaning and disinfection of ISO 5 PEC takes place at the beginning of each shift, after spills, when contamination is suspected and at least every 30 minutes during continued compounding activity.			
Cleaning and disinfection of counters and floors takes place at least daily.			
Cleaning and disinfection of walls, ceilings and storage shelving takes			

place at least monthly.			
Cleaning materials (i.e. mops, sponges, wipes) are nonshedding and dedicated to cleanroom, ante-area and buffer area and are not removed from these areas.			
Cleaning and disinfection of work surfaces in direct compounding areas includes removing debris (i.e. water soluble residue with sterile water) then disinfecting with a proper disinfecting agent such as sterile 70% IPA. Disinfecting agents are allowed to dry before beginning compounding.			
Training and Evaluation of Aseptic Manipulation			
Audio-visual instruction and professional publications are utilized to train personnel who prepare CSPs with regard to theoretical principles, practical skills, and achieving and maintaining an ISO 5 environment. Personnel must also pass a written competence assessment and undergo an observational audit. This training takes place before personnel are allowed to prepare CSPs.			
Observational audits evaluate garbing and gloving techniques including proper hand hygiene. The observational audit is documented on a form and maintained in a permanent record.			
Observational audits which evaluate cleaning and disinfection competency are performed for all staff responsible for cleaning and disinfection. This competency assessment is performed initially, when cleaning staff changes and at the completion of any media fill test. A form is used to document the observation.			
Personnel are required to pass media fill tests prior to preparing CSPs initially and at least annually for low and medium risk compounding and semiannually for high risk			

compounding.			
Compounding personnel who fail written, observational or media fill tests are promptly reinstructed and re-evaluated by qualified compounding personnel.			
Gloved fingertip sampling is performed initially prior to compounding CSPs (no less than 3 times) and at least annually (for low and medium risk compounding) and semiannually (for high risk compounding). This assessment is performed immediately after the evaluation of hand hygiene and garbing (above).			
An evaluation of aseptic manipulation takes place for all compounding personnel initially and annually (for low and medium risk compounding) and semiannually (for high risk compounding).			
Training includes instruction on how to determine if equipment is operating properly.			
Quality Assurance (QA)			
Facility has formal QA program in place that is formalized in writing.			
Written policies and procedures detail the training and evaluation of compounding personnel.			
Written policies and procedures include in-process checks that are applied, as appropriate, to specific CSPs: accuracy and precision of measuring and weighing, sterility, methods of sterilization and purification, safe limits and ranges for strength of ingredients, bacterial endotoxins, particulate matter, pH, labeling accuracy and completeness, BUD assignment, packaging and storage requirements.			
Written policies and procedures outline compounding procedures and sterilization of CSPs			
Written policies and procedures detail			

equipment use, calibration, maintenance and proper function.			
Certification of PECs is performed by a qualified individual and takes place every 6 months and whenever the device and/or room is relocated or service is performed. Documentation is kept on file.			
Certification that each ISO 5,7, and 8 area meets guidelines for total particle counts takes place every 6 months and whenever a PEC is relocated or when alteration of the buffer or ante areas take place. Tests are performed by qualified personnel using state-of-the-art equipment. Documentation is kept on file. Thresholds for total particle counts follow threshold requirements set forth in USP 797.			
Environmental sampling (ES), including viable and nonviable testing occurs as part of a quality assurance program: 1. at the initial certification of new equipment or facility 2. after equipment or facility is serviced 3. every 6 months as part of recertification of equipment and facility 4. when work practice problems are identified or suspected with products or staff			
A viable airborne particle testing program is in place (regardless of compounding risk level) and is utilized in combination with observational audits which are designed to evaluate the competency of staff . Plan includes sample location, method of collection, volume of air sampled, time and frequency of sampling.			
Viable air samples are taken from locations within the ISO 5,7 and 8 environments which are most prone to contamination.			
Viable air sampling of each separate			

compounding area within the facility is performed by properly trained individuals (impaction is the preferred method of viable air sampling) at least semiannually and when facilities and/or equipment are re-certified			
An investigation is conducted for cfu counts or employee audits/competency evaluations that are out of the normal range and the source of the problem is eliminated.			
Surface sampling is performed in all ISO areas on a regular basis.			
A pressure gauge or velocity meter is installed between the buffer area and anteroom and between the anteroom and the area outside the compounding area. Results are documented on a log at least daily or by a continuous reading device. Pressure readings between areas follow requirements set forth in USP 797.			
Automatic compounding devices (ACDs) are tested at least daily for accuracy. Results are documented and reviewed at least weekly to ensure precision of the ACD.			
All CSPs are visually inspected for particulate matter and reviewed for accuracy (prescription orders, compound records, expended materials). The process for inspection of final CSPs is outlined in policies and procedures. This includes a process for double-checking each CSP immediately prior to release.			
Facility has written procedures for verifying the identity and quality of CSP prior to dispensing. The procedure includes the following: 1. labels is correct and reflects the correct names, amounts, volume, BUD, route, storage and other information for safe use. 2. Correct identity, purity and amounts of ingredients are			

verified by comparing the finished CSP to the original written order			
Drug storage areas are monitored to ensure proper storage conditions of ingredients. Controlled temperature areas (i.e. refrigerated, room temperature and frozen) are monitored at least daily and results are documented on a temperature log.			
Standard operating procedures exist to ensure storage conditions in patient-care settings are appropriate.			
Caregiver training is in place to ensure understanding and compliance with CSP use. Training includes: 1. Description of the therapy, goals of therapy and expected outcomes 2. How to inspect CSPs, supplies and equipment 3. Handling and storage of all drugs and supplies 4. How to check labels prior to administration 5. Proper administration including aseptic technique 6. Catheter care 7. How to monitor for and detect complications 8. What to do in the case of an emergency 9. Proper waste disposal			
Hazardous Drug CSPs			
Hazardous drugs are prepared as CSPs only under conditions that protect the person who is compounding them.			
Hazardous drugs are stored separate from non-hazardous inventory, preferably in a negative pressure area. The storage area should have sufficient exhaust ventilation with at least 12 air changes per hour. Access to the storage area is limited.			
Hazardous drugs are handled using appropriate chemotherapy gloves			

including during stocking, receiving, preparation and disposal.			
Hazardous drugs are prepared in an ISO 5 environment or better in a protective engineering control following aseptic practices. Access to the preparation area is limited.			
Hazardous drugs are prepared in a BSC or CACI. The BSC or CACI is an ISO 5 environment placed in an ISO 7 area, physically separate from other preparation areas. The ISO 7 area optimally is a negative pressure area that has not more than 0.01 inch water column negative pressure to the adjacent room (a pressure gauge is installed to ensure adequate pressure).			
The BCS or CACI is 100% vented to the outside via a HEPA filter to protect the environment.			
When CSTDs are used to prepare hazardous preparations they are used within an ISO 5 BSC or CACI located in an ISO 7 negative pressure area as per above (In facilities that prepare a small volume of hazardous preparations the use of a CSTD within an ISO 5 BSC or CACI located in a negative pressure area is acceptable).			
Personnel who compound hazardous preparations utilize appropriate PPE. Personnel should double glove with sterile chemotherapy-appropriate gloves.			
All personnel who compound hazardous preparations are properly trained in the storage, handling and disposal of hazardous substances. Training occurs prior to the preparation of hazardous drugs and its effectiveness is verified by testing of technique annually. This verification is documented.			
Hazardous drug preparation training includes didactic summary of mutagenic, teratogenic and			

carcinogenic properties. Training also includes aseptic technique, negative pressure technique, proper CSTD use, hazardous drug disposal and cleanup of hazardous material spills. Training also includes treatment of staff that have come in contact with hazardous materials.			
Disposal of hazardous drug waste complies with all federal and state regulations.			
Personnel of child bearing ability are required to provide written verification that they understand the risks of working with hazardous drugs.			
Radiopharmaceuticals			
Radiopharmaceuticals prepared from sterile components with a volume of 100ml or less for single doses and 30ml or less for multiple dose containers conform to the specific recommendations set forth for low-risk level CSP compounding. These preparations are compounded in an ISO 5 PEC located within an ISO 8 environment			
Technetium-99m vials which were punctured in an ISO 5 environment with a sterile needle may be used up to the time allotted according to manufacturer recommendations			
Radiopharmaceuticals classified as low risk CSPs with 12 hour or less BUD are prepared in a separated compounding area defined by a line of demarcation.			
Allergen extracts			
Allergen extracts meet the requirements set forth in the *CSP Microbial Contamination Risk Levels* section of USP 797 except where they meet the following criteria: 1. compounding involves only simple transfer of sterile, commercial allergen products 2. All allergen extracts contain sufficient, appropriate amounts of ingredients for the			

prevention of microorganism growth 3. Compounding personnel perform thorough hand-cleaning prior to preparing allergen extracts including utilization of a nail cleaner and warm water. Hands and arms are washed up to the elbows for at least 30 seconds with soap and water. Alcohol-based hand gel is used during persistent activity 4. Hair covers, facial hair covers, gowns and masks are used to compound allergen extracts 5. Powder-free sterile gloves are used during compounding 6. Gloves are disinfected with sterile 70% IPA when multiple extracts are prepared as CSPs 7. Necks of ampuls and stoppers of vials are disinfected by wiping with sterile 70% IPA and allowing to sit for at least 10 seconds before air drying prior to use 8. Proper aseptic technique is used to compound allergen extracts as CSPs 9. Multidose vials of allergen extracts list the specific patient name, BUD and storage temperature range 10. Single dose allergen extract CSPs are not stored for any period of time for future use.			
Low Risk Level Compounding (specific requirements)			
CSPs are compounded entirely within ISO 5 or better environment using sterile ingredients and devices			
In the absence of sterility testing, storage periods for compounded CSPs do not exceed: • Not more than 48 hours at room temperature • Not more than 14 days			

refrigerated • Not more than 45 days in solid frozen state			
Quality assurance practices include: • Routine disinfection and air quality testing of the direct compounding area • Visual confirmation of proper garbing of compounding personnel • Review of orders and ingredient packages of compounded items • Visual inspection of CSPs to ensure no particulate matter is present			
Personnel authorized to compound in a low-risk environment are required to pass written and media fill tests prior to preparing CSPs initially and at least annually. Personnel who fail the tests are immediately re-instructed and re-evaluated by qualified compounding personnel.			
Low Risk Level Compounding with 12 hour or less BUD (specific requirements)			
Only low risk, nonhazardous and radiopharmaceutical CSPs which are patient-specific and made according to a physician's order are prepared			
Administration occurs within 12 hours of preparation or per manufacturer recommendations, whichever is less.			
PEC is certified to maintain an ISO 5 environment			
PEC is located in a segregated compounding area. This area is restricted to sterile compounding activity. This segregated area does not contain unsealed windows or doors that lead to the outdoors or high traffic areas. This area is not adjacent to a warehouse, construction site or food preparation.			
Sinks are not located adjacent to the ISO 5 PEC device.			
Cleaning and disinfection procedures,			

personnel training, competency evaluation of garbing, aseptic work practices and viable and nonviable environmental sampling procedures follow recommendations set forth in USP 797.			
Quality assurance practices include: • Routine disinfection and air quality testing of the direct compounding area • Visual confirmation of proper garbing of compounding personnel • Review of orders and ingredient packages of compounded items • Visual inspection of CSPs to ensure no particulate matter is present and CSP is properly labeled.			
Personnel authorized to compound in a low-risk environment are required to pass written and media fill tests prior to preparing CSPs initially and at least annually. Personnel who fail the tests are immediately re-instructed and re-evaluated by qualified compounding personnel.			
Medium Risk Level Compounding (specific requirements)			
In the absence of sterility testing, storage periods for compounded CSPs do not exceed: • Not more than 30 hours at room temperature • Not more than 9 days refrigerated • Not more than 45 days in solid frozen state			
Quality assurance procedures include all of those outlined for low risk compounding and include a more 'challenging' media fill test performed at least annually (such as that suggested in USP 797).			
Personnel authorized to compound in a medium-risk environment are required to pass written and media fill			

tests prior to preparing CSPs initially and at least annually. Personnel who fail the tests are immediately re-instructed and re-evaluated by qualified compounding personnel.			
High Risk Level Compounding(specific requirements)			
Sterilization methods used for CSPs maintain the labeled strength of the active ingredients and integrity of packaging			
Water-containing CSPs that are nonsterile during ANY phase of preparation are sterilized within 6 hours of preparation of the final product.			
In the absence of sterility testing, storage periods for compounded CSPs do not exceed: • Not more than 24 hours at room temperature • Not more than 3 days refrigerated • Not more than 45 days in solid frozen state			
Non-sterile devices are rinsed thoroughly with sterile, pyrogen-free water then 'drained and dried immediately' prior to use for high risk compounding			
All high risk CSP solutions are passed through a filter no larger than 1.2 micron before or during filling into their final containers.			
Sterilization of high risk CSPs by filtration are required to utilize a 0.2 micron filter and takes place entirely within an ISO class 5 or better environment			
Quality assurance procedures include all of those for low-risk level compounding and include a more challenging media fill test (such as that suggested in USP 797). This media fill test is performed semiannually by each person authorized to compound high risk CSPs.			
Personnel authorized to compound in			

a high-risk environment are required to pass written and media fill tests prior to preparing CSPs initially and at least semiannually. Personnel who fail the tests are immediately re-instructed and re-evaluated by qualified compounding personnel.			
All high risk CSPs prepared in groups of 25 identical packages or more or those which are in multi-dose vials for administration to multiple patients or that are exposed for longer than 12 hours at 2° to 8°C or longer than 6 hours at warmer than 8°C before sterilization undergoes sterility testing as described in chapter 71 of USP before they are dispensed. A written procedure requiring daily observation of incubation is written to detail the process when high risk level CSPs are dispensed prior to receiving the results of the sterility tests.			
All high risk CSPs (except those for inhalation and ophthalmic administration) prepared in groups of 25 identical packages or more or in multi-dose vials for administration to multiple patients or that are exposed for longer than 12 hours at 2° to 8°C or longer than 6 hours at warmer than 8°C before sterilization are tested for bacterial endotoxins.			

FDA

Enforcement Report

EXHIBIT 305

The FDA Enforcement Report is published weekly by the Food and Drug Administration, Department of Health and Human Services. It contains information on actions taken in connection with agency Regulatory activities.

April 30, 2003
03-18

RECALLS AND FIELD CORRECTIONS: FOODS - CLASS II

PRODUCT
Yellow Fin Tuna - Vacuum packaged. Recall # F-331-3.
CODE
The product was uncoded.
RECALLING FIRM/MANUFACTURER
Schneider's Fish & Seafood Corp, Cheektowaga, NY, by telephone, and letter on July 27, 2001. FDA initiated recall is complete.
REASON
Unlabeled product and lack of assurance of proper temperature controls during thawing.
VOLUME OF PRODUCT IN COMMERCE
110 lbs.
DISTRIBUTION
NY.

PRODUCT
Paradise Brand; Cryo-Freeze Tuna Steaks. Recall # F-332-3.
CODE
a) Burris Lot #89892;
b) Burris Lot #87869;
c) Americold Lot #25282.
RECALLING FIRM/MANUFACTURER
Ocean Duke Corporation, Torrance, CA, by email on December 16, 2001, and by telephone and faxed letters on December 18, 2001. Firm initiated recall is complete.
REASON
Vacuum-packaged tuna loins were inadequately labeled resulting in the potential for the formation of C. botulinum toxin due to temperature abuse.
VOLUME OF PRODUCT IN COMMERCE
a) 2,500 cases of 6/8 oz;
b) 3,300 cases of 6/8 oz;
c) 795 cases of 8/10 oz.
DISTRIBUTION
NY, MD, OH, IL, and MA.

PRODUCT
Springfield Smoked Fish Co., Inc. Brand:
Vacuum Packed

Recall # F-334-3;
b) Smoked Lemon Peppered Mackerel Fillets.
Various Wts. from 14-10.0 lbs. Recall # F-335-3;
c) Smoked Mackerel Fillets. Various wts. .94-15.15 lbs.
Recall # F-336-3;
d) Smoked Bluefish Fillets. Various wts. from .79-50.01
lbs. Recall # F-337-3;
5 Lb. and 8 oz tubs purchased prior to 3/9/02:
e) Smoked White Fish. Recall # F-338-3;
f) Smoked White Fish Salad. Recall # F-339-3.

CODE

a) Mfg. Code #48;
b) Mfg. Code #47;
c) Mfg. Code #17;
d) Mfg. Code #11;
5 Lb. and 8 oz tubs purchased prior to 3/9/02:
e) Smoked White Fish;
f) Smoked White Fish Salad.

RECALLING FIRM/MANUFACTURER

Springfield Smoked Fish Co., Inc. Springfield, MA, by letter March 15, 2002. Firm initiated recall is complete.

REASON

Products may be underprocessed.

VOLUME OF PRODUCT IN COMMERCE

a) 43.04 lbs;
b) 21.19 lbs;
c) 21.51 lbs;
d) 71.38 lbs;
e) Undetermined;
f) Undetermined.

DISTRIBUTION

MA, CO, and NJ.

PRODUCT

Vacuum packed fish products as follows:
a) Cold Smoked CR King. Recall # F-340-3;
b) Cold Smoked Bellies. Recall # F-341-3;
c) Cold Smoked Trim. Recall # F-342-3;
d) CR King Lox Sides. Recall # F-343-3;
e) Cold Smoked Nova Lox. Recall # F-344-3;
f) Cold Smoked Nova Side. Recall # F-345-3;
g) King Salmon Lox Sides. Recall # F-346-3;
h) Cold Smoked Portions. Recall # F-347-3;
i) Cold Smoked Lox KS. Recall # F-348-3.

CODE

All products on the market during the time the recall was initiated.

RECALLING FIRM/MANUFACTURER

Smoki Foods, Inc., Seattle, WA, by telephone and letter on August 20, 2002, and by another letter on August 22, 2002. FDA initiated recall is complete.

REASON

The products may not have adequate water phase salt levels resulting in the potential for C. botulinum toxin formation.

VOLUME OF PRODUCT IN COMMERCE

12,441 lbs.

DISTRIBUTION

WA, and HI.

RECALLS AND FIELD CORRECTIONS: DRUGS - CLASS I

PRODUCT
Ancom tablets, Anti-hypertensive Compound Tablets, 100 count bottle. The exterior holding carton is labeled in a similar manner with a paper insert labeled in part as --Ancom tablet is a complex preparation consisting of anti-hypertensive agents such as rauwolfia alkaloid, dihydralazine sulphate, together with sedative, diuretic, blood-potassium equilibrium salt, etc. Each tablet contains: Reserpine 0.032 mg, Potassium Chloride 30 mg, Hydrochlorothiazide 3.1 mg, Vitamin B1 1 mg, Diazepam 1 mg, Promethiazine HCL 2.1 mg, Dihydralazine Sulphate 4.2 mg, Calcium pantothenate 1 mg, Magnesium Trisilicate 30 mg, Vitamin B6. The bottle, unit carton & insert are labeled both in English and Chinese. Recall # D-233-3.
CODE
All lot codes.
RECALLING FIRM/MANUFACTURER
Recalling Firm: Herbsland Incorporated, New York, NY, by visit, on November 22, 2002.
Manufacturer: Shanghai Pharmaceutical Industry Corp. Shanghai, China. FDA initiated recall is complete.
REASON
Unapproved new drug labeled to contain several prescription drug ingredients, including reserpine, diazepam, promethiazine, and hydrochlorothiazide.
VOLUME OF PRODUCT IN COMMERCE
300 bottles.
DISTRIBUTION
NY.

PRODUCT
Ancom tablets, Anti-hypertensive Compound Tablets, 100 count bottle. The exterior holding carton is labeled in a similar manner with a paper insert labeled in part as --Ancom tablet is a complex preparation consisting of anti-hypertensive agents such as rauwolfia alkaloid, dihydralazine sulphate, together with sedative, diuretic, blood-potassium equilibrium salt, etc. Each tablet contains: Reserpine 0.032 mg, Potassium Chloride 30 mg, Hydrochlorothiazide 3.1 mg, Vitamin B1 1 mg, Diazepam 1 mg, Promethiazine HCL 2.1 mg, Dihydralazine Sulphate 4.2 mg, Calcium pantothenate 1 mg, Magnesium Trisilicate 30 mg, Vitamin B6. The bottle, unit carton & insert are labeled both in English and Chinese. Recall # D-234-3.
CODE
All lot codes.
RECALLING FIRM/MANUFACTURER
Recalling Firm: Best Life International, Incorporated, Mayaguez, PR, by letter, on February 11, 2003.
Manufacturer: Shanghai Pharmaceutical Industry Corp. Shanghai, China. FDA initiated recall is ongoing.
REASON
Unapproved New Drug containing several prescription ingredients.
VOLUME OF PRODUCT IN COMMERCE
591 bottles.
DISTRIBUTION
Nationwide

RECALLS AND FIELD CORRECTIONS: DRUGS - CLASS II

PRODUCT
a) Betamethasone Repository Injection, 6 mg/mL, 2, 5 and 10mL glass vials, Rx. Recall # D-227-3;
b) Betamethasone Repository (PF) Injection, 6 mg/mL, 2, 5 and 10mL glass vials, Rx. Recall # D-228-3.
CODE
a) Lot Number: 12102002@11, 09172002@1, 10012002@5, 10212002@10, 10282002@8, 11162002@1, 11262002@6, 12012002@19, 01022003@23, 01072003@12, 01102003@3, 01162003@7;
b) Lot Numbers: 01022003@24, 01282003@1.
RECALLING FIRM/MANUFACTURER
New England Compounding Center, Framingham, MA, by telephone on February 21, 2003, and letters on February 28, 2003. Firm initiated recall is ongoing.
REASON

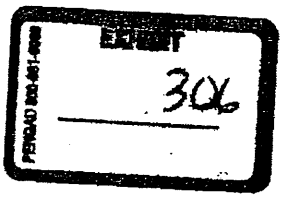
VOLUME OF PRODUCT IN COMMERCE
a) 4,362 vials;
b) 9 vials.
DISTRIBUTION
Nationwide

RECALLS AND FIELD CORRECTIONS: DRUGS - CLASS III

PRODUCT
Necon 0.5/35 Tablets (norethindrone 0.5mg and ethinyl estradiol 35mcg), 6 tablet dispensers, 28 tablets each, Rx only.
Recall # D-185-3.
CODE
Lot 50701D00, Exp April 2003.
RECALLING FIRM/MANUFACTURER
Watson Diagnostics, Inc, by letter on January 9, 2003. Firm initiated recall is ongoing.
REASON
Impurities; product exceeds total impurities specification (stability).
VOLUME OF PRODUCT IN COMMERCE
6,366 cartons.
DISTRIBUTION
Nationwide.

PRODUCT
a) Methylprednisolone AC (PF) Injection, 80mg/mL,
1 mL vial, Rx only. Recall # D-215-3;
b) Methylprednisolone AC (PF) Injection, 40mg/mL,
1 mL vial, Rx only. Recall # D-217-3.
CODE
a) Lot Codes: 04172002@7, 04112002@8, 03282002@10,
03122002@12, 02272002@8, 02132002@1, 02052002@6
04292002@5, 05072002@17, 05192002@15, 05232002@3
05312002@16, 07042002@2;
b) Lot codes: 04182002@1, 06032002@16.
RECALLING FIRM/MANUFACTURER
New England Compounding Center, Framingham, MA, by telephone between July 2002 and August 2002. Firm initiated recall is complete.
REASON
Product labeled with incorrect expiration date.
VOLUME OF PRODUCT IN COMMERCE
a) 9,551 - 1mL vials;
b) 861 - 1 mL.
DISTRIBUTION
Nationwide.

PRODUCT
Allegra Tablets, 60/120mg, 60 count bottles, Rx only.
Recall # D-220-3.
CODE
Lot # 3B1250BA EXP 5/2004 Lot # 3B1250BB EXP 5/2004.
RECALLING FIRM/MANUFACTURER
Recall by: Direct Dispensing, Inc., Miami, FL, by telephone on March 26, 3003, and by letters on April 3, 2003.
Manufactured by: Aventis Pharmaceuticals, Kansas City, MO.
Firm initiated recall is ongoing.
REASON
Mislabeled (by repacker); bottle labeled to contain Allegra actually contains Allegra-D (fexofenadine/pseudoephedrine



Inspections, Compliance, Enforcement, and Criminal Investigations

New England Compounding Center 04-Dec-06

Department of Health and Human Services

Public Health Service
Food and Drug Administration

New England District
One Montvale Avenue
Stoneham, Massachusetts
02180
(781) 596-7700
FAX: (781) 596-7896

WARNING LETTER

NWE-06-07W
VIA FEDERAL EXPRESS

December 4, 2006

Barry J. Cadden, Director of Pharmacy and Owner
New England Compounding Center
697 Waverly Street
Framingham, MA 01702

Dear Mr. Cadden:

On September 23, 2004, investigators from the U.S. Food and Drug Administration (FDA) and the Massachusetts Board of Pharmacy inspected your firm, located at 697 Waverly Street, Framingham, Massachusetts. On January 19, 2005, the inspection was completed. This inspection revealed that your firm compounds human prescription drugs in various dosage forms and strengths.

We acknowledge the receipt of your October 1, 2004, letter addressed to FDA's New England District Office, concerning questions presented during the referenced inspection.

FDA's position is that the Federal Food, Drug, and Cosmetic Act (FDCA) establishes agency jurisdiction over "new drugs," including compounded drugs. FDA's view that compounded drugs are "new drugs" withi the meaning of 21 U.S.C. § 321(p), because they are not "generally recognized, among experts . . . as safe and effective," is supported by substantial judicial authority. See Weinberger v. Hynson, Westcott & Dunning, 412 U.S. 609, 619, 629-30 (1973) (explaining the definition of "new drug"); Prof'ls & Patients for tomized Care v. Shalala, 56 F.3d 592, 593 n.3 (5th Cir. 1995) (the FDCA does not expressly exempt pharmacies or compounded drugs from its new drug provisions); In the Matter of Establishment Inspectio of: Wedgewood Village Pharmacy, 270 F. Supp. 2d 525, 543-44 (D.N.J. 2003), aff'd, Wedgewood Village Pharmacy v. United States, 421 F.3d 263, 269 (3d Cir. 2005) ("The FDCA contains provisions with explicit exemptions from the new drug . . . provisions. Neither pharmacies nor compounded drugs are expressly exempted."). FDA maintains that, because they are "new drugs" under the FDCA, compounded drugs may not be introduced into interstate commerce without FDA approval.

efficacy. However, FDA has long recognized the important public health function served by traditional pharmacy compounding. FDA regards traditional compounding as the extemporaneous combining, mixing, or altering of ingredients by a pharmacist in response to a physician's prescription to create a medication tailored to the specialized needs of an individual patient . See Thompson v. Western States Medical Center, 535 U.S. 357, 360-61 (2002). Traditional compounding typically is used to prepare medications that are not available commercially, such as a drug for a patient who is allergic to an ingredient in a mass-produced product, or diluted dosages for children.

Through the exercise of enforcement discretion, FDA historically has not taken enforcement actions against pharmacies engaged in traditional pharmacy compounding. Rather, FDA has directed its enforcement resources against establishments whose activities raise the kinds of concerns normally associated with a drug manufacturer and whose compounding practices result in significant violations of the new drug, adulteration, or misbranding provisions of the FDCA.

FDA's current enforcement policy with respect to pharmacy compounding is articulated in Compliance Policy Guide (CPG), section 460.200 ["Pharmacy Compounding"], issued by FDA on May 29, 2002 (see Notice of Availability, 67 Fed. Reg. 39,409 (June 7, 2002)).[1] The CPG identifies factors that the Agency considers in deciding whether to initiate enforcement action with respect to compounding. These factors help differentiate the traditional practice of pharmacy compounding from the manufacture of unapproved new drugs. They further address compounding practices that result in significant violations of the new drug, adulteration, or misbranding provisions of the FDCA. These factors include considering whether a firm compounds drugs that are copies or essentially copies of commercially available FDA-approved drug products without an FDA sanctioned investigational new drug application (IND). The factors in the CPG are not intended to be exhaustive and other factors may also be appropriate for consideration.

1. Copies of Commercially Available Druo Products:

It has come to our attention that you are compounding trypan blue ophthalmic products. During the inspection at your firm, you advised an investigator from FDA's New England District Office that the trypan blue products that your firm compounds are devices. FDA classifies trypan blue products as drugs, not devices. Further, on December 16, 2004, trypan blue ophthalmic solution was approved by FDA and it is commercially available. As stated in the CPG, FDA will not exercise its enforcement discretion for the compounding of copies of commercially available FDA-approved products, including this one.

We have also learned that your firm may be compounding 20% aminolevulinic acid solution (ALA). Please note that there is a commercially available, FDA-approved aminolevulinic acid solution 20% . Like compounded trypan blue, FDA regards compounded 20% aminolevulinic acid solution as a copy of commercially available drug.

Although Section 503A of the FDCA (21 U.S.C. § 353a) addresses pharmacy compounding, this provision was invalidated by the Supreme Court's ruling in Thompson v. Western States Medical Center, 535 U.S. 357 (2002), that Section 503A included unconstitutional restrictions on commercial speech . And those restrictions could not be severed from the rest of 503A. In Thompson v. Western States Medical Center, 535 U.S. 357 (20020), the Supreme Court affirmed the Ninth Circuit ruling that the provisions in question violated the First Amendment.

FDA does not sanction the compounding of copies of FDA-approved, commercially available drugs and the agency will not exercise its enforcement discretion regarding the trypan blue and ALA products compounded by your firm.

All products compounded by your firm containing trypan blue or ALA are drugs within the meaning of section 201(g) of the FDCA (21 U.S.C. § 321(g)). These products are misbranded under section 502(f)(1) of the FDCA (21 U.S.C. § 352(f)(1)) in that their labeling fails to bear adequate directions for their use. They are not exempt from this requirement under 21 CFR § 201 .115 because they are new drugs within the meaning of section 201(p) of the FDCA and they lack approved applications filed pursuant to section 505 of the FDCA (21 U.S.C. § 355).

2. Anesthetic Drug Products

Equally serious, your firm's promotional materials reveal that it offers to compound "Extra Strength Triple Anesthetic Cream" which contains 20% benzocaine, 6% lidocaine, and 4% tetracaine. Like a manufacturer you have developed a standardized anesthetic drug product that you sell under the name "Extra Strength Triple Anesthetic cream," Further, you generate sales by giving physicians "courtesy prescriptions" (i.e., [illegible] the traditional practice of pharmacy compounding, in

prescriptions from licensed practitioners to meet the unique medical needs of individual patients.

Moreover, the agency is concerned with the public health risks associated with the compounding of "Extra Strength Triple Anesthetic Cream." There have been at least two nonfatal reactions and two deaths attributed to the use of compounded topical local anesthetic creams containing high doses of local anesthetics. Local anesthetics, like "Extra Strength Triple Anesthetic Cream," may be toxic at high dosages, and this toxicity can be additive. Further, there is a narrow difference between the optimal therapeutic dose of these products and the doses at which they become toxic, i.e. they have low therapeutic index.

Adverse events consistent with high systemic exposures to these products include seizures and cardiac arrhythmias. Specifically, risk of systemic adverse events from tetracaine products includes (1) a systemic allergic response to p-aminobenzoic acid (PABA) which, at worst, could lead to cardiac arrest; or (2) excessive systemic absorption following repetitive or extensive application, especially for a 4%a product, which could ultimately lead to convulsions. Tetracaine is associated with a higher incidence of allergic reactions than other anesthetics, such as lidocaine. The risk of systemic toxicity is greatest in small children and in patients with preexisting heart disease. Factors that may increase systemic exposure are time and surface area of the exposure, particularly when the area of application is covered by an occlusive dressing. Benzocaine has an additional toxicity not seen with (idocaine, methemoglobinemia, an acquired decrease in the oxygen-carrying capacity of the red blood cells. Further, patients with severe hepatic disease are at greater risk of developing toxic plasma concentrations of local anesthetics because of their inability to metabolize them.

The Extra Strength Triple Anesthetic Cream compounded by your firm is a drug within the meaning of section 201(g) of the FDCA (21 U.S.C. § 321(g)). This product is misbranded under section 502(f)(1) of the FDCA (21 U.S.C. § 352(f)(1)) in that its labeling fails to bear adequate directions for its use. It is not exempt from this requirement under 21 CFR § 201.115, because it is a new drug within the meaning of section 201(p) of the FDCA that lacks an approved application filed pursuant to section 505 of the FDCA U.S.C. § 355).

Depending on its labeling, this product may also violate section 502(a) of the FDCA (21 U.S.C. § 352(a)). A drug or device is misbranded under section 502(a) if its labeling is false and misleading in any particula (e.g., if the labeling for your local anesthetic products fails to reveal the consequences that may result from the use of the product as a local anesthetic).

3. Repackaging:

Additionally, we are in receipt of a complaint alleging that you are repackaging the approved injectable drug, Avastin, into syringes for subsequent promotion and sale to health professionals . Avastin is unpreserved and is packaged and labeled in 4 and 16 ml single-use glass vials. The labeled precautions include "discard any unused portion left in a vial . . . ." Each step in the manufacture and processing of a new drug or antibiotic, from handling of raw ingredients to final packaging, must be approved by FDA, whether carried out by the original manufacturer or by some subsequent handler or repacker of the product. Pharmacists are not exempt from these statutory requirements. Generally, the agency regards mixing, packaging, and other manipulations of approved drugs by licensed pharmacists, consistent with the approved labeling of the product, as an approved use of the product if conducted within the practice of pharmacy, i.e., filling prescriptions for identified patients. However, processing and repacking (including repackaging) of approved drugs is beyond the practice of pharmacy and is thus subject to the Act's premarket approval requirements.

The agency has an established policy, articulated in Compliance Policy Guide Sec. 446.100, Regulatory Action Regarding Approved New Drugs and Antibiotic Drug Products Subjected to Additional Processing or other Manipulations (CPG 7132c.06) (copy enclosed), concerning the manipulation of approved sterile drug products outside the scope of the FDA-approval. FDA is particularly concerned about the manipulation of sterile products when a sterile container is opened or otherwise entered to conduct manipulations. The moment a sterile container is opened and manipulated, a quality standard (sterility) is destroyed and previous studies supporting the standard are compromised and are no longer valid. We are especially concerned with the potential microbial contamination associated with splitting Avastin - a single-use, preservative-free, vial -- into multiple doses. When used intravitreally, microbes could cause endophthalmitis, which has a high probability for significant vision loss. The absence of control over storage, and delays before use after repackaging, only exacerbate these concerns.

Avastin is approved for use in the treatment of colorectal cancers. The text of your alleged promotional

such; your firm is distributing an unapproved new drug in violation of section 505 of the FDCA. Because the product lacks adequate labeling for its intended use (see 21 CFR § 201.128) your firm is also distributing a misbranded drug in violation of section 502(f)(1) of the FDCA (21 U.S.C. § 352(f)(1)). Also, please note that, under section 301(a) of the FDCA (21 U.S.C. § 331(a)), the introduction or delivery for introduction into interstate commerce of any drug that is misbranded is prohibited.

Under section 301(d) of the FDCA (21 U.S.C. § 331(d)), the introduction or delivery for introduction into interstate commerce of a new drug that has not been approved under section 505 is also prohibited.

Further, we have been informed that, although your firm advises physicians that a prescription for an individually identified patient is necessary to receive compounded drugs, your firm has reportedly also told physicians' offices that using a staff member's name on the prescription would suffice. Drugs compounded in this manner are not compounded consistent with the CPG, and FDA will not exercise its enforcement discretion regarding those drugs.

The above violations are not intended to be an all-inclusive list of deficiencies. You should take prompt action to correct these deviations. Failure to promptly correct these deviations may result in additional regulatory action without further notice, including seizure or injunction against you and your firm. Federal agencies are routinely advised of the issuance of warning letters so that they may take this information into account when considering the award of government contracts.

Please notify this office in writing within 15 working days of receipt of this letter of any steps that you wil take to correct the noted violations, including an explanation of the steps taken to prevent the recurrence of similar violations. If corrective action cannot be completed within 15 working days, please state the reason for the delay and the time within which the correction will be complete.

You should address your reply to this letter to the U.S. Food and Drug Administration, New England District Office, One Montvale Ave., 411 Floor, Stoneham, MA 02180, Attn: Ann Simoneau, Compliance Officer. If you have any further questions, please feel free to contact Ms. Simoneau at (781) 596-7732.

Sincerely,

/s/

Gail Costello
District Director
New England District Office

Page Last Updated: 07/08/2009
Note: If you need help accessing information in different file formats, see Instructions for Downloading Viewers and Players.

U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
Ph. 1-888-INFO-FDA (1-888-463-6332)
Contact FDA

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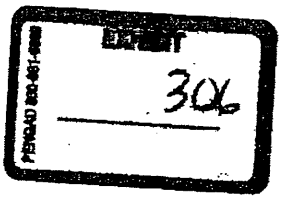

Inspections, Compliance, Enforcement, and Criminal Investigations

New England Compounding Center 04-Dec-06

Department of Health and Human Services

Public Health Service
Food and Drug Administration

New England District
One Montvale Avenue
Stoneham, Massachusetts
02180
(781) 596-7700
FAX: (781) 596-7896

WARNING LETTER

NWE-06-07W
VIA FEDERAL EXPRESS

December 4, 2006

Barry J. Cadden, Director of Pharmacy and Owner
New England Compounding Center
697 Waverly Street
Framingham, MA 01702

Dear Mr. Cadden:

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We acknowledge the receipt of your October 1, 2004, letter addressed to FDA's New England District Office, concerning questions presented during the referenced inspection.

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efficacy. However, FDA has long recognized the important public health function served by traditional pharmacy compounding. FDA regards traditional compounding as the extemporaneous combining, mixing, or altering of ingredients by a pharmacist in response to a physician's prescription to create a medication tailored to the specialized needs of an individual patient . See Thompson v. Western States Medical Center, 535 U.S. 357, 360-61 (2002). Traditional compounding typically is used to prepare medications that are not available commercially, such as a drug for a patient who is allergic to an ingredient in a mass-produced product, or diluted dosages for children.

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FDA's current enforcement policy with respect to pharmacy compounding is articulated in Compliance Policy Guide (CPG), section 460.200 ["Pharmacy Compounding"], issued by FDA on May 29, 2002 (see Notice of Availability, 67 Fed. Reg. 39,409 (June 7, 2002)).[1] The CPG identifies factors that the Agency considers in deciding whether to initiate enforcement action with respect to compounding. These factors help differentiate the traditional practice of pharmacy compounding from the manufacture of unapproved new drugs. They further address compounding practices that result in significant violations of the new drug, adulteration, or misbranding provisions of the FDCA. These factors include considering whether a firm compounds drugs that are copies or essentially copies of commercially available FDA-approved drug products without an FDA sanctioned investigational new drug application (IND). The factors in the CPG are not intended to be exhaustive and other factors may also be appropriate for consideration.

1. Copies of Commercially Available Druo Products:

It has come to our attention that you are compounding trypan blue ophthalmic products. During the inspection at your firm, you advised an investigator from FDA's New England District Office that the trypan blue products that your firm compounds are devices. FDA classifies trypan blue products as drugs, not devices. Further, on December 16, 2004, trypan blue ophthalmic solution was approved by FDA and it is commercially available. As stated in the CPG, FDA will not exercise its enforcement discretion for the compounding of copies of commercially available FDA-approved products, including this one.

We have also learned that your firm may be compounding 20% aminolevulinic acid solution (ALA). Please note that there is a commercially available, FDA-approved aminolevulinic acid solution 20% . Like compounded trypan blue, FDA regards compounded 20% aminolevulinic acid solution as a copy of commercially available drug.

Although Section 503A of the FDCA (21 U.S.C. § 353a) addresses pharmacy compounding, this provision was invalidated by the Supreme Court's ruling in Thompson v. Western States Medical Center, 535 U.S. 357 (2002), that Section 503A included unconstitutional restrictions on commercial speech . And those restrictions could not be severed from the rest of 503A. In Thompson v. Western States Medical Center, 535 U.S. 357 (20020), the Supreme Court affirmed the Ninth Circuit ruling that the provisions in question violated the First Amendment.

FDA does not sanction the compounding of copies of FDA-approved, commercially available drugs and the agency will not exercise its enforcement discretion regarding the trypan blue and ALA products compounded by your firm.

All products compounded by your firm containing trypan blue or ALA are drugs within the meaning of section 201(g) of the FDCA (21 U.S.C. § 321(g)). These products are misbranded under section 502(f)(1) of the FDCA (21 U.S.C. § 352(f)(1)) in that their labeling fails to bear adequate directions for their use. They are not exempt from this requirement under 21 CFR § 201 .115 because they are new drugs within the meaning of section 201(p) of the FDCA and they lack approved applications filed pursuant to section 505 of the FDCA (21 U.S.C. § 355).

2. Anesthetic Drug Products

Equally serious, your firm's promotional materials reveal that it offers to compound "Extra Strength Triple Anesthetic Cream" which contains 20% benzocaine, 6% lidocaine, and 4% tetracaine. Like a manufacturer you have developed a standardized anesthetic drug product that you sell under the name "Extra Strength Triple Anesthetic cream," Further, you generate sales by giving physicians "courtesy prescriptions" (i.e., [illegible] with the traditional practice of pharmacy compounding in

prescriptions from licensed practitioners to meet the unique medical needs of individual patients.

However, the agency is concerned with the public health risks associated with the compounding of "Extra Strength Triple Anesthetic Cream." There have been at least two nonfatal reactions and two deaths attributed to the use of compounded topical local anesthetic creams containing high doses of local anesthetics. Local anesthetics, like "Extra Strength Triple Anesthetic Cream," may be toxic at high dosages, and this toxicity can be additive. Further, there is a narrow difference between the optimal therapeutic dose of these products and the doses at which they become toxic, i.e. they have low therapeutic index.

Adverse events consistent with high systemic exposures to these products include seizures and cardiac arrhythmias. Specifically, risk of systemic adverse events from tetracaine products includes (1) a systemic allergic response to p-aminobenzoic acid (PABA) which, at worst, could lead to cardiac arrest; or (2) excessive systemic absorption following repetitive or extensive application, especially for a 4%a product, which could ultimately lead to convulsions. Tetracaine is associated with a higher incidence of allergic reactions than other anesthetics, such as lidocaine. The risk of systemic toxicity is greatest in small children and in patients with preexisting heart disease. Factors that may increase systemic exposure are time and surface area of the exposure, particularly when the area of application is covered by an occlusive dressing. Benzocaine has an additional toxicity not seen with (idocaine, methemoglobinemia, an acquired decrease in the oxygen-carrying capacity of the red blood cells. Further, patients with severe hepatic disease are at greater risk of developing toxic plasma concentrations of local anesthetics because of their inability to metabolize them.

The Extra Strength Triple Anesthetic Cream compounded by your firm is a drug within the meaning of section 201(g) of the FDCA (21 U.S.C. § 321(g)). This product is misbranded under section 502(f)(1) of the FDCA (21 U.S.C. § 352(f)(1)) in that its labeling fails to bear adequate directions for its use. It is not exempt from this requirement under 21 CFR § 201.115, because it is a new drug within the meaning of section 201(p) of the FDCA that lacks an approved application filed pursuant to section 505 of the FDCA U.S.C. § 355).

Depending on its labeling, this product may also violate section 502(a) of the FDCA (21 U.S.C. § 352(a)). A drug or device is misbranded under section 502(a) if its labeling is false and misleading in any particula (e.g., if the labeling for your local anesthetic products fails to reveal the consequences that may result from the use of the product as a local anesthetic).

3. Repackaging:

Additionally, we are in receipt of a complaint alleging that you are repackaging the approved injectable drug, Avastin, into syringes for subsequent promotion and sale to health professionals . Avastin is unpreserved and is packaged and labeled in 4 and 16 ml single-use glass vials. The labeled precautions include "discard any unused portion left in a vial . . . ." Each step in the manufacture and processing of a new drug or antibiotic, from handling of raw ingredients to final packaging, must be approved by FDA, whether carried out by the original manufacturer or by some subsequent handler or repacker of the product. Pharmacists are not exempt from these statutory requirements. Generally, the agency regards mixing, packaging, and other manipulations of approved drugs by licensed pharmacists, consistent with the approved labeling of the product, as an approved use of the product if conducted within the practice of pharmacy, i.e., filling prescriptions for identified patients. However, processing and repacking (including repackaging) of approved drugs is beyond the practice of pharmacy and is thus subject to the Act's premarket approval requirements.

The agency has an established policy, articulated in Compliance Policy Guide Sec. 446.100, Regulatory Action Regarding Approved New Drugs and Antibiotic Drug Products Subjected to Additional Processing or other Manipulations (CPG 7132c.06) (copy enclosed), concerning the manipulation of approved sterile drug products outside the scope of the FDA-approval. FDA is particularly concerned about the manipulation of sterile products when a sterile container is opened or otherwise entered to conduct manipulations. The moment a sterile container is opened and manipulated, a quality standard (sterility) is destroyed and previous studies supporting the standard are compromised and are no longer valid. We are especially concerned with the potential microbial contamination associated with splitting Avastin - a single-use, preservative-free, vial -- into multiple doses. When used intravitreally, microbes could cause endophthalmitis, which has a high probability for significant vision loss. The absence of control over storage, and delays before use after repackaging, only exacerbate these concerns.

Avastin is approved for use in the treatment of colorectal cancers. The text of your alleged promotional

such your firm is distributing an unapproved new drug in violation of section 505 of the FDCA. Because the product lacks adequate labeling for its intended use (see 21 CFR § 201.128) your firm is also distributing a misbranded drug in violation of section 502(f)(1) of the FDCA (21 U.S.C. § 352(f)(1)). Also, please note that, under section 301(a) of the FDCA (21 U.S.C. § 331(a)), the introduction or delivery for introduction into interstate commerce of any drug that is misbranded is prohibited.

Under section 301(d) of the FDCA (21 U.S.C. § 331(d)), the introduction or delivery for introduction into interstate commerce of a new drug that has not been approved under section 505 is also prohibited.

Further, we have been informed that, although your firm advises physicians that a prescription for an individually identified patient is necessary to receive compounded drugs, your firm has reportedly also told physicians' offices that using a staff member's name on the prescription would suffice. Drugs compounded in this manner are not compounded consistent with the CPG, and FDA will not exercise its enforcement discretion regarding those drugs.

The above violations are not intended to be an all-inclusive list of deficiencies. You should take prompt action to correct these deviations. Failure to promptly correct these deviations may result in additional regulatory action without further notice, including seizure or injunction against you and your firm. Federal agencies are routinely advised of the issuance of warning letters so that they may take this information into account when considering the award of government contracts.

Please notify this office in writing within 15 working days of receipt of this letter of any steps that you wil take to correct the noted violations, including an explanation of the steps taken to prevent the recurrence of similar violations. If corrective action cannot be completed within 15 working days, please state the reason for the delay and the time within which the correction will be complete.

You should address your reply to this letter to the U.S. Food and Drug Administration, New England District Office, One Montvale Ave., 411 Floor, Stoneham, MA 02180, Attn: Ann Simoneau, Compliance Officer. If you have any further questions, please feel free to contact Ms. Simoneau at (781) 596-7732.

Sincerely,

/s/

Gail Costello
Disrict Director
New England District Office

Page Last Updated: 07/08/2009
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ASHP Guidelines on Outsourcing Sterile Compounding Services

Purpose

Health care organizations considering outsourcing sterile compounding services should have a clear understanding of what they want to accomplish. Consideration should include, at the least, an internal needs assessment, a cost analysis, and a careful review of prospective compounding pharmacies. The organization should examine the potential long-term consequences of outsourcing as well as the short-term outcomes expected during a contract's performance period.

The purpose of these guidelines is to provide an overview of factors and processes for health care organizations to consider when exploring outsourcing of pharmacy sterile compounding. The ideas presented in this document could be used for strategic planning with the organization's decision-makers, for drafting contract provisions, for comparing prospective compounding pharmacies, for preparing for contract negotiations, or for evaluating a compounding pharmacy's performance.

This document includes ideas about reasons for outsourcing and reasons for not outsourcing, services available from compounding pharmacies, the outsourcing process and outsourcing arrangements, and evaluation of a compounding pharmacy's performance. The appendix provides a topical list of contract provisions, some of which relate to practices that are the subject of other American Society of Health-System Pharmacy (ASHP) guidelines. Organizations should refer to pertinent ASHP guidelines for additional information on which to base their contract provisions, agreements, and decisions.[1-3] This document addresses representative outsourcing options and contract agreements and is not intended to cover all situations. Managers of pharmacy and health care organizations should use their professional judgment about applicability to their own needs and circumstances.

Environment

There are various environmental influences and market forces that may contribute to a facility's decision to consider outsourcing. A list of some of those considerations follows.

Organizational and Operational

- Limited available technological resources to provide the specific desired services.
- Re-engineering and downsizing initiatives.
- Consolidation and integration of health systems and departments within health systems.
- Elimination of or reduction in the size of traditional pharmacy departments.
- Reorganization around patient-focused care.
- Implementation of automated pharmacy systems and the attendant need to reorganize medication preparation and distribution functions.

Staffing

- Shortage of pharmacists, nurses, and other health care professionals.
- Shortage of pharmacy personnel with specific experience and capabilities.

Financial and Cost Control

- Restricted budgets.
- Increased operating costs.
- Increased drug costs.
- Increased emphasis on measuring performance in terms of staffing and costs.

Quality Assurance

- Increased expectations of and pressures from payers, accreditation organizations, and consumer groups to improve the quality of patient care, reduce the incidence of hospital infections, and demonstrate compliance with applicable standards and regulations.

Governmental and Regulatory

- Reductions of federal, state, and local government reimbursement for health care.
- Increased numbers of individuals dependent on federal, state, and local governments for health care.
- Increased federal and state interest in standards for sterile compounding (i.e., *United States Pharmacopeia* [*USP*] chapter 797[4]).

Competitive

- Increased competition among healthcare organizations.
- Increased competition among suppliers of pharmaceutical products and related services.

Purposes of Outsourcing

Health care organizations that conduct in-depth assessments may decide that outsourcing either is or is not a good option for meeting their needs. Reasons for their decision will vary according to a variety of factors.

Reasons Health Care Organizations Outsource Sterile Compounding Services. Organizations tend to outsource sterile compounding services when guided by a careful assessment of their capabilities of providing services themselves, when unsuccessful in using their own resources to provide those services, or, in some cases, upon advice from a consultant. Contracting with an outsourcing firm may produce one or more of the following results.

Organizational and Operational

- Ease the consolidation of pharmaceutical services in integrated health systems.

- Resolve operational inefficiencies (e.g., batch compounding, staff scheduling, high-demand periods).
- Provide compounded preparations outside the scope of preparations routinely provided (e.g., complex or rarely compounded preparations).
- Enable the organization to acquire additional resources and expertise to carry out other priorities (e.g., reallocation of existing staff to roles in patient care areas).

Staffing

- Help the organization to staff hard-to-fill pharmacy positions and address staffing vacancies.
- Allow the organization to reach optimal staffing levels for achieving productivity targets.

Financial and Cost Control

- Control or reduce the cost of the organization's services (e.g., by shifting costs associated with i.v. admixture production from fixed to variable).
- Control or reduce labor costs (e.g., by shifting responsibility for employees, benefits, and liabilities to a compounding pharmacy).
- Enable the organization to acquire a business partner to share the risks and other associated liability by defining the responsibilities associated with operating sterile compounding services.
- Minimize the cost of facility remodeling (e.g., to meet *USP* 797 requirements).

Quality Assurance

- Provide consistent pharmacy and sterile compounding services, including documented beyond-use dating.
- Enable the organization to maintain or improve the quality of patient care (e.g., by expanding clinical services or establishing new services).
- Provide support for the medical and nursing staffs and improve physician–nursing–pharmacy collaboration.
- Improve organizational procedures by learning from the compounding pharmacy's experience and knowledge, especially with new technologies (e.g., labeling, bar-coding, or tamper-evidence technologies).

Governmental and Regulatory

- Assist and ensure compliance with legal, regulatory, certification, and accreditation requirements.

Competitive

- Allow the organization to gain an edge on competitors through improvements in service, quality, or price.

Reasons Health Care Organizations Do Not Outsource Sterile Compounding Services. An organization's choice to continue providing its own sterile compounding services may be based on one or more of the following reasons.

Organizational and Operational

- The organization demonstrates that its sterile compounding services are cost-effective, well managed, and provided as efficiently as or better than they could be by a compounding pharmacy.
- Negative experiences with outsourcing pharmacy (or even nonpharmacy) services, or awareness of other organizations' negative experiences with such outsourcing.
- Concern about time delays in receiving compounded preparations, especially products that are needed urgently or have poor stability or short beyond-use times.
- Concern that the compounding pharmacy may experience interruptions in service, perhaps with little notice, due to quality-control issues not related to services provided to the organization.
- Concern that the decision to outsource sterile compounding services can be reversed only with great difficulty.
- Concern about losing short-term and long-term control over decisions regarding or expertise in sterile compounding services.

Staffing

- Concern that staff will be reduced to unacceptable levels.

Financial and Cost Control

- An assessment that outsourcing would increase rather than decrease costs.
- Concern that high-cost drugs might be excluded from contract agreements.
- Concern that the organization may not be able to recapitalize sterile compounding services if outsourcing is unsuccessful.

Quality Assurance

- Concern that conflicting values and priorities of the compounding pharmacy and the organization will reduce quality.
- Concern about the qualifications or competencies of compounding pharmacy staff.

Professional Responsibility

- Concern that outsourcing sterile compounding will confuse or dilute the onsite pharmacists' ultimate professional and legal authority and responsibility for other medication-related activities and outcomes at the site.

Services Provided by Compounding Pharmacies

The needs of the health care organization should guide the identification of potential compounding pharmacies with the appropriate expertise and capabilities. Among the services that may be available from compounding pharmacies are

the preparation of implantable and external pump cartridges; total parenteral nutrition, dialysis, irrigation, or cardioplegia solutions; antibiotics; ophthalmic injectables and solutions; chemotherapy preparations; and analgesic preparations (patient-controlled analgesia, epidural, or regional nerve-block devices).

Compounding pharmacies are regulated in a number of ways. They may be registered as pharmacies and/or wholesalers in the states in which they dispense, as drug establishments and/or device manufacturers by the Food and Drug Administration (FDA), and/or as manufacturers by the Drug Enforcement Administration (DEA). FDA requires a device manufacturer registration for a compounding pharmacy to dispense devices such as dialysate solutions or heparin or citrate syringes. A compounding pharmacy registered as a drug establishment may apply for a labeler code that allows it to create National Drug Code (NDC) numbers for its products. These NDC numbers do not indicate FDA approval or that a New Drug Application has been filed, nor do they indicate a higher degree of quality (e.g., that terminal sterilization rather than an aseptic fill process has been used in compounding the preparation). Ascertaining that a preparation is labeled with an NDC number is therefore not a substitute for the due diligence required to verify a compounding pharmacy's quality processes (e.g., *USP* 797, current good manufacturing processes). Finally, compounding pharmacies are not permitted to prepare copies of commercial products. Dispensing of such products by compounding pharmacies will result in regulatory action, as FDA enforcement discretion does not apply to copies of commercial products.

Outsourcing Process

After the health care organization has completed an internal assessment of its needs and capabilities and decided to explore outsourcing, it should identify and contact reputable compounding pharmacies. Organizations that are part of a larger network (e.g., an integrated delivery network) may explore options that are available to them through the network or from other organizations in the network.

Some organizations simply identify prospective compounding pharmacies and ask them to submit a proposal. A more thorough approach is to require prospective compounding pharmacies to respond to a request for proposal (RFP). Although a formal RFP (and the compounding pharmacy's formal proposal based on the RFP) may not be necessary, the information found in typical RFPs and proposals may be helpful for making a decision about outsourcing.

Contents of RFPs. RFPs often include the following information:

- A description of the demographics of the organization making the RFP (e.g., number of hospitals, bed sizes, typical census).
- A description of the process the organization will use to select the compounding pharmacy.
- The organization's standard terms and conditions for contracting for services or, if available, a sample contract from the organization.
- The names and telephone numbers of individuals in the organization who are involved in the outsourcing decision (the organization's director of pharmacy should be included).
- A description of the specific services required of the compounding pharmacy (e.g., volume, intravenous admixture preparation, automated pharmacy systems, existing intravenous delivery systems and devices) and performance-measurement criteria or targets.
- The dates on which the organization's representatives can inspect the compounding pharmacy's facility, with reasonable notice.
- The number of copies of the proposal to submit.
- The name and address of the individual to whom the proposal is to be delivered.
- Acceptable methods for delivery of the proposal (e.g., e-mail, mail, delivery service, courier).
- A statement that the organization reserves the right to cancel its solicitation for services and reject any and all proposals.
- A deadline date and time for receipt of the proposal.
- The date on which the compounding pharmacy would be expected to initiate services.
- The date by which the selected compounding pharmacy must provide a written contract.
- Other requirements related to the proposal (e.g., that it be in a specific file format, include reference to an RFP number [if any], or be signed by an officer of the firm who is authorized to contract or his or her designee).

Contents of Proposals. RFPs should require prospective compounding pharmacies to submit the following information with their proposals:

- A brief history of the compounding pharmacy, including its mission, vision, and values.
- The location of the compounding pharmacy's offices and other facilities that would provide services to the organization.
- The compounding pharmacy's regular business hours or hours of operation and emergency and after-hours contact information.
- The names, addresses, telephone numbers, and résumés or background information on individuals who will provide the outsourced services.
- Assurance that all pharmacists employed at the compounding facility are licensed as required.
- Evidence of the following documentation regarding the compounding pharmacy:
  - Proof of current liability insurance.
  - Current accreditation or certification certificates, if applicable.
  - State pharmacy licensure and other appropriate licenses.
  - Licensure documents if the compounding pharmacy is registered with FDA as a drug establishment or device manufacturer.
  - Current DEA registration as a manufacturer or wholesaler.
  - Licensure of pharmacists employed and verification that they are in good standing on file and available for review.
  - Registration of pharmacy technicians employed and verification that they are in good standing on file and available for review, if applicable.

  - Pharmacist and pharmacy technician notarized statements stating they have never been convicted of a drug-related misdemeanor or felony on file and available for review.
  - Standard operating procedures manual on file and available for review.
  - Pharmacist training manual on file and available for review.
  - Pharmacy technician training manual on file and available for review.
  - Policies and procedures for sterility testing on file and available for review.
  - Policies and procedures for pyrogen testing on file and available for review, if applicable.
  - Examples of batch reports for products being considered for outsourcing.
  - Examples of the quality-control reports.
  - Stability documents and clinical references, as well as any materials that are used to determine beyond-use dates.
- A history of the results of all accreditation or regulatory surveys conducted of the compounding pharmacy's sites, including copies of significant regulatory actions.
- Proof of professional liability, general liability, and workers' compensation insurance coverage (including the name, address, and telephone number of the insurance company).
- Experience (e.g., years of experience in providing sterile compounding services, total number of clients served, current number of clients).
- A list of the requested services that the compounding pharmacy can provide and the normal terms of service, including but not limited to normal delivery cycles, availability and cost of emergency preparation and delivery, remedies for failure to perform to the contract, specific goods and services to be provided, and the infrastructure available at the compounding pharmacy for electronic ordering.
- A list of the requested sterile compounding services that the compounding pharmacy cannot provide and the reasons for its inability to provide them.
- A copy of a standard or proposed contract.
- A list of all fees and charges, including shipping, handling, and delivery charges, and any fees associated with order changes that would be billed under the contract and the billing methodology for their calculation.
- A billing schedule and a copy of a sample bill for each of the preparations compounded by the compounding pharmacy.
- A description of a routine delivery schedule (e.g., daily by a specified time) and options for nonroutine delivery (e.g., later the same day, after hours, weekends, holidays, during emergencies).
- Examples of reports that the compounding pharmacy will be expected to submit to the organization.
- Information relating to the compounding pharmacy's financial status and stability (e.g., balance sheets and audited financial statements for the past three years, bank references, lists of principal equity owners).
- The process for requesting new preparations from the compounding pharmacy.
- The names, addresses, and telephone numbers of
  - Current clients of a similar size or receiving similar types of compounded preparations, with written references and copies of annual performance-improvement reports, if possible.
  - Reference accounts served within the past two years and the reasons for all, if any, terminations of services.

Additional information to obtain from the prospective compounding pharmacy but not necessarily contained in the proposal may include

- Whether the compounding pharmacy has had product liability lawsuits filed against it for preparations it compounded. If so, the compounding pharmacy should be asked to provide a description of the lawsuits filed, the file date of the lawsuits, and the outcome.
- A description of the compounding pharmacy's formal procedures for conducting recalls and whether there have ever been recalls of any of its compounded preparations. If the compounding pharmacy has ever recalled any of its compounded preparations, it should be asked to provide the dates of recall, a description of the preparations recalled, and the reasons for the recall.
- Information related to the delivery process (especially in the case of severe weather).

Visits to Compounding Pharmacies and Their Clients. Compounding pharmacies should allow the organization's representatives to visit their corporate offices and compounding facilities. The compounding pharmacy should provide ample opportunity for the organization's representatives to confer with the compounding pharmacy's corporate, pharmacy, and compounding staff.

Evaluating Proposals. A decision to outsource sterile compounding services should be collaborative and may involve, as appropriate, the governing board, the chief executive officer (CEO), the chief financial officer (CFO), the chief operating officer (COO), the chief of the medical staff, the chair of the pharmacy and therapeutics (P&T) committee, the director of nursing (DON), the director of pharmacy, legal counsel, and department heads, for example. The organization should scrutinize the following factors when evaluating proposals:

- Services offered versus services requested (including the compounding pharmacy's potential to enhance currently offered sterile compounding services).
- Professional experience (e.g., years of service; number, size, and types of clients; knowledge of the organization's operations).
- Quality management program, specifically as it relates to facility cleaning and validation, staff training, and competency assessment.
- Financial stability (e.g., ability to absorb start-up expenses and to commit the resources needed to initiate service),
- References and reputation.
- Information systems and other technological infrastructure (e.g., the capability to interface with the organization's information and drug delivery systems, such

as infusion pumps or bar-coded medication administration systems).
- Demonstrated commitment to continually integrating technology and knowledge to improve patient safety.
- Education and training of compounding pharmacy's staff (e.g., internal and external continuing-education programs, educational allowances for professional and technical staff).
- The organization's and the compounding pharmacy's policies on specific compounding practices (e.g., references with real-time stability data supporting beyond-use dating, compliance with standards and regulations, use of USP–NF-grade ingredients or FDA-approved products in accordance with the organization's intended use).
- Risk assessment program to ensure that medication errors are not introduced by new or increased outsourced compounding activities and that the medications dispensed are compatible with the client's medication administration devices (e.g., bar-code labeling, smart pumps).
- Knowledge of the regulatory requirements and accreditation standards that the customer must meet and willingness to assist customers in meeting these standards.
- Inventory and supply chain issues (e.g., the organization's and compounding pharmacy's back-order policies).
- Emergency-preparedness implications (e.g., the ability of the organization and the compounding pharmacy to deliver services in the event of a disaster).
- Additional qualities (e.g., high employee morale, confidentiality, creativity, dedication to the community, collaborative spirit).
- Cost aspects of services (e.g., cost-effectiveness, ability to achieve economies of scale).

The compounding pharmacy should, at a minimum, be able to

- Provide assurance that each compounded sterile preparation meets applicable state and federal labeling requirements and is sterile and free of pyrogens and unintended particulate matter, according to professionally established and accepted quality monitoring data.
- If the compounding pharmacy is compounding high-risk preparations, provide documentation of the end-product testing processes used to determine that compounded sterile preparations are sterile and free of pyrogens and unintended particulate matter.
- Deliver appropriate compounded preparations in tamper-resistant packaging and in containers that will maintain proper storage temperature and (when required) protection from light during delivery and storage.
- Provide, upon request, batch records for any compounded sterile preparation.

The organization should assign an evaluation rating to each proposal. Ratings should be weighted appropriately with respect to services, experience, references, and cost. The organization should base its decision to outsource sterile compounding services on its assessment of the compounding facility's ability to meet the organization's needs and fulfill the terms of the contract.

Outsourcing Arrangement. The health care organization and the compounding facility should agree on the outsourcing arrangement that best meets their needs. The contract should clearly describe all aspects of the outsourcing arrangement. The health care organization's pharmacy should

- Ensure that the proper body of the health care organization (e.g., the organization's P&T committee) has developed a formal process to identify which preparations will (and which preparations will not) be prepared by the compounding pharmacy, based on the therapeutic needs of patients and logistical considerations associated with using a compounding pharmacy.
- Establish the components of the medication order or prescription.
- Determine whether patient consent must be obtained for use of preparations compounded outside the health care organization's pharmacy, consistent with state board of pharmacy regulations and prevailing law.
- Ensure that the agreement and the compounding pharmacy facility have been reviewed by all the necessary bodies in the pharmacy's health care organization (e.g., the organization's risk management team, legal counsel, P&T and infection control committees, epidemiology department staff).
- Determine how to handle situations in which a patient presents with a compounded medication that neither the health care organization's pharmacy nor the compounding pharmacy prepares under the existing agreement (e.g., medication in an implantable device, i.v. push medication, i.v. infusion) and that has not been previously considered by the P&T committee. Considerations include what the process will be for
  - Having the P&T committee consider outsourcing the compounding of such medications to a compounding pharmacy.
  - Acquiring such medications from a compounding pharmacy that the health care organization does not have an agreement with and how the associated liability risks will be addressed until the P&T committee decision is obtained regarding such medications.
  - Continuing to acquire such medications if the compounding pharmacy already under contract cannot or will not prepare them and how the associated liability risks will be addressed (e.g., whether the health care organization's pharmacy will negotiate an agreement with another compounding pharmacy that does compound the preparation) until the P&T committee decision is obtained regarding such medications.

Negotiating the Contract. The health care organization should carefully review the proposal and clarify the provisions of the contract. Active participation by the health care organization's risk management and legal counsel is highly recommended. Negotiations can ensure a contract that best meets the needs of the health care organization and the compounding pharmacy. ASHP believes that the health care organization's pharmacist-in-charge (e.g., a pharmacy director) must take complete responsibility for patient outcomes from all medication-related activities performed at or for the

organization's work sites, whether they are carried out by the organization's staff or by off-site contractors. This responsibility should be explicitly stated in all outsourcing contracts.

The signed contract between the parties should at a minimum

- Describe the term length of the agreement and the processes for the compounding pharmacy's billing to the health care organization, including methods of determining the charge for the compounded items, payment terms, and processes for resolution of disputed invoices.
- Contain a confidentiality clause and a Health Insurance Portability and Accountability Act business associate agreement, if applicable.
- Establish the pharmacy's right to inspect the premises of the compounding facility at any time with reasonable notice, including the right to inspect quality-control reports.
- Describe the method of communicating the medication order or prescription from the health care organization's pharmacy to the compounding pharmacy (e.g., telephone, fax, computer transmission, hard copy, electronic DEA form 222).
- Protect the health care organization from liabilities created by errors made by the compounding pharmacy and delineate the obligations of both parties.
- Establish preparation recall procedures that comply with hospital policy mandates and prevailing law should a preparation need to be recalled by the compounding pharmacy.
- Address documentation, regulatory and accreditation compliance, sterile compounding process, and compounded preparation considerations.
- Describe the pertinent situations and processes for the return of compounded preparations to the compounding pharmacy.
- Describe any requirements regarding the submission of quality reports by the compounding pharmacy.
- Describe the procedures for resolving preparation or delivery issues encountered by the organization or the compounding pharmacy.
- Describe the contents of ancillary agreements or addenda to the contract (e.g., the "expectations agreement" between the organization and the compounding pharmacy).

Organizations often find it convenient to outline expectations that are subject to frequent change in an addendum to the contract, because that allows the addendum to be updated rather than the entire contract. If such terms are not included in the contract, the expectation agreement should

- Delineate routine sterile compounding turnaround times (e.g., from receipt of the medication order or prescription by the compounding pharmacy to delivery to the health care organization) and describe acceptable deviations from the agreed-upon schedules (e.g., raw product availability problems, unique end-product testing requirements, compounded preparation stability characteristics, nonroutine and emergency requests).
- Describe the specific drugs provided, documentation flow, delivery methods, security considerations, and time frames for the provision of controlled substances by the compounding pharmacy.
- Describe any special processes, documentation flow, delivery methods, security considerations, and time frames for the provision of hazardous drugs by the compounding pharmacy.

Signing the Contract. In some organizations the director of pharmacy may be authorized to sign contracts for outsourced services. If this is not the case, the director of pharmacy must be fully involved in negotiating the contract and advising the authorized signers.

Contract Provisions

A contract that meets the needs of the health care organization and of the compounding pharmacy is the foundation for a successful relationship. Contracts should specifically describe the respective responsibilities of the organization and the compounding pharmacy. See the appendix for examples of contract provisions.

Evaluation of Compounding Pharmacy's Performance

The health care organization should evaluate and document the compounding pharmacy's performance and assess the compounding pharmacy's compliance with the terms of the contract. The compounding pharmacy should regularly submit quality reports, and the organization should regularly perform objective and subjective evaluations (e.g., quarterly, annually). Evaluations should address all measurable standards of performance specified in the contract. Evaluations should be multidisciplinary and should involve, for example, the CEO, CFO, COO, DON, and medical staff representatives, as appropriate. An evaluation may include an assessment of how well the compounding pharmacy has

- Improved the quality of patient care.
- Responded to the organization's needs (e.g., invoicing, process adjustment).
- Helped the organization achieve its financial and patient-outcome goals.
- Improved the productivity and performance of pharmacy staff.
- Improved pharmacy processes (e.g., medication dispensing and delivery).
- Reduced and controlled pharmacy costs without compromising patient care.
- Worked and communicated effectively with the organization's staff and resolved problems.

Handling Performance or Quality Issues

The compounding pharmacy should provide the health care organization with information at least quarterly on its compliance with contract requirements and other information needed for the organization's quality-assurance programs. A mechanism should be in place for resolving preparation or delivery issues (e.g., delivery to the wrong location, late deliveries).

Conclusion

These guidelines offer an overview of factors and processes for health care organizations to consider when exploring the outsourcing of pharmacy sterile compounding. Such considerations include an internal needs assessment, a cost analysis, a careful review of prospective compounding pharmacies, and an examination of the potential long-term consequences of outsourcing as well as the short-term outcomes expected during a contract's performance period. The ideas presented can be used for strategic planning, drafting of initial contract provisions, comparing prospective compounding pharmacies, preparing for contract negotiations, or evaluating a compounding pharmacy's performance. These guidelines are intended to address representative outsourcing options and contract agreements and may not be applicable to all situations. Managers of pharmacy and health care organizations should exercise professional judgment about applicability to their own needs and circumstances.

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Appendix—Contract Provisions

The following are examples of contract provisions that, among others, the organization and a compounding pharmacy might adapt as needed and include in a contract, depending on the scope of services being considered. In addition, a contract would include provisions about the specific compounding services to be provided by the compounding pharmacy. The language in contract provisions should always be adapted to meet the specific needs of the health care organization and to comply with the organization's contracting policies and applicable laws and regulations.

In reviewing the following list of suggested contract provisions, attention should be paid to the fact that listed provisions are not intended and should not be considered all-inclusive and do not constitute legal advice but rather are provided solely to convey general information related to legal issues commonly addressed in contracts for the outsourcing of sterile compounding services. The purpose of enumerating the following possible contract provisions is to provide a general understanding of the types of provisions that may be included in a contract. Because laws vary from jurisdiction to jurisdiction and are subject to varying interpretations, health care organizations considering outsourcing sterile compounding services should consult with professional legal counsel in their relevant jurisdictions regarding the drafting of contracts.

Accreditation and Certification. A contract should include a requirement that services meet or exceed applicable accreditation and certification standards. These include, but are not limited to, the standards (or requirements) of the following organizations.

- The Joint Commission
- American Osteopathic Association
- Center for Medicare and Medicaid Services
- Pharmacy Compounding Accreditation Board

After-Hours Access. This section describes the process and extent of access to off-site compounding pharmacy resources after normal business hours.

Choice of Law. The contract should state that the contract is governed by the laws of the state in which patient care is provided.

Compounding Pharmacy Indemnification. This section describes in detail the indemnities the compounding pharmacy owes the health care organization, such as

> Contractor shall indemnify and defend Customer and its Affiliates, and each of their respective officers, directors, trustees, employees, agents, and representatives (collectively, the "Customer Indemnities") and hold them harmless from and against any and all Losses on account of any Claims asserted by a third party in connection with, arising from, or related to (a) any of the

acts or omissions to this Agreement attached hereto, (b) breach of Contractor's representations, (c) injuries to persons, including death, or damage to property caused by Contractor's agents, servants, or employees, or in any way attributable to Contractor's performance and prosecution of this Agreement, and (d) any sexual harassment or other illegal sexual advances upon any of Customer's employees, contractors, agents, or other personnel by any of Contractor's employees, independent contractors, or other personnel.

Compounding Pharmacy Performance Responsibilities. The off-site compounding center's responsibilities and commitments associated with proper federal and state licensure and regulatory requirements for all the preparations it compounds are outlined in this section (e.g., labeling). It further describes the compounding center's responsibilities to operate in accordance with applicable Good Manufacturing Practices, Drug Enforcement Agency (DEA) requirements (as applicable), *United States Pharmacopeia* (*USP*) 797 requirements, and company standard operating procedures.

Compounding Pharmacy Reports. The content and regularity of performance reports that the compounding pharmacy will submit to the organization may be specified.

Confidential Information. This section describes what information is considered confidential and actions that are required to prevent unauthorized distribution of such information. Both parties must agree to safeguard access to computer databases and patient records to ensure that the patient's rights to privacy and confidentiality are protected. Use of the information should be limited solely to purposes specified in the contract.

Customer Responsibilities. This section describes the health-system pharmacy's responsibilities for affirming that it has all required state, local, and federal licenses associated with the receipt of services being provided by the off-site compounding pharmacy. It may also describe the health care organization's responsibilities for determining clinical appropriateness of any compounded preparation it purchases from an off-site compounding pharmacy as well as the procedures to be used to ensure the traceability of compounded preparations.

Extension of Period of Performance. Conditions for extending the period of performance should be included in the contract.

Force Majeure. This section describes when neither party shall be liable for nonperformance or delays related to causes that are beyond one's reasonable control.

Forms. Responsibilities for the design, approval, purchase, and storage of forms may be assigned.

General Provisions. This section outlines a myriad of other contractual items, such as contract assignment, process for adding or changing compounding services, reference to other agreements, and reference to other applicable terms outside of the services agreement.

Hazardous Drug Preparations. Responsibilities for ensuring the safety of the organization's staff and patients during delivery and distribution of hazardous drug preparations may be assigned. Either the organization or the compounding pharmacy should provide a hazardous materials handling program, including staff training, that meets ASHP guidelines and Occupational Safety and Health Administration (OSHA) requirements.

Indemnification. This section describes specific conditions under which both parties will hold each other harmless for, and potentially defend, the actions of the other.

Information Transfer. This section describes the mechanisms by which the organization transfers orders and other information to the compounding pharmacy.

Laws, Rules, and Regulations. Requirements for services to meet or exceed federal, state, and local laws, rules, and regulations may be specified. These include but are not limited to those of FDA, DEA, OSHA, *USP*, and the state board of pharmacy. The compounding pharmacy should maintain (e.g., display, file) the appropriate licenses, permits, and records of equipment maintenance and certification. Any compounding pharmacy required to be licensed as a manufacturer must be so licensed.

Liability Insurance. This section describes the responsibility for maintaining liability insurance coverage. The contract might specify, for example, the specific level of liability insurance coverage that the health care organization and the compounding pharmacy must maintain.

Payment Terms. This section describes the agreed-upon number of days from receipt of an invoice by the health care organization's pharmacy until payment is due to the compounding pharmacy.

Period of Performance. This section specifies the period for which the compounding pharmacy will provide services to the organization.

Pricing. The price of each service the hospital pharmacy is interested in purchasing from the off-site compounding pharmacy along with conditions and methodology for price increases is described in this section. Shipping, handling, and delivery charges for both routine and non-routine deliveries should also be detailed.

Policies and Procedures. This section describes the required written policies and procedures covering the outsourced services, all of which should comply with applicable laws, regulations, and accreditation or certification standards. The contract should specify that the policies and procedures must not conflict with those of the organization.

Record Maintenance. The contract should specify that all pertinent records must be kept for the time required by law and by the organization and describe how, where, and by whom the record will be maintained.

Requirements. This section establishes a mutual understanding of annual purchase volume commitments between the health care organization's pharmacy and the compounding pharmacy.

Staff Education and Training. Responsibilities for required ongoing staff or compounding pharmacy education and training may be specified. For example, there might be an agreement that the compounding pharmacy's staff will participate in some of the organization's education and training programs. In addition, the compounding pharmacy may agree to provide specific training to ensure that all compounding pharmacy and health care organization personnel can perform the duties created by the compounding pharmacy's services.

Successors. The rights of each party in the event that the health care organization or compounding pharmacy merges or transfers its business or assets to a successor should be addressed in a contract.

Term of Agreement. This section communicates the length of time the agreement is in effect between the health care organization and the compounding pharmacy, including renewals.

Termination. This section describes how and when the contract will end or be terminated, including early termination. It should also address any penalties which may be appropriate or when the contract may be ended without penalty.

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EXHIBIT
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Letter 8/11/15

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Tel: 800.994.6322 or 508.820.0606
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General Overview of Policies & Procedures for Compounding Sterile Products

NECC operates in accordance with the following general guidelines when compounding sterile products:

A. Facility/Equipment

a. Class 10 Microenvironments (barrier isolator).
b. Certified by Massachusetts Board of Pharmacy as a pharmacy with a central venous admixture service (CIVAS) in accordance with Board regulations, 247 CMR 6.01 (6) (c).

B. Monitoring & Maintenance

Class 10 Microenvironments validated every 6 months by an independent vendor.

C. Personnel

a. All sterile compounding is performed by properly trained and validated registered pharmacists.
b. Pharmacy personnel are trained/validated by an outside agency, Professional Compounding Centers of America (PCCA).
c. Personnel are validated on a quarterly basis.

D. Quality Assurance/Quality Control

a. USP Chemicals are obtained only from FDA registered facilities.
b. Formulations are sterilized by either filtration through a 0.22 micron filter or by autoclaving.
c. Samples from final product batch lots are sent to an independent FDA registered analytical lab for sterility, endotoxin (pyrogenicity) and potency testing.
d. Tested medication is quarantined and dispensed only after the sample has tested negative for endotoxin and microbial contamination.
e. The Quality Assurance Team (QAT), made up of employees from all departments within NECC, meets regularly to review all quality related items.

f. NECC maintains strict environmental testing protocols. Results of these tests are reported at all QAT meetings.
g. All sterile compounding actions are performed in compliance with NECC's Standard Operating Procedures (SOPs). These SOPs have been "mapped" against USP 797 "Pharmaceutical Compounding – sterile preparations" to ensure that all USP 797 requirements are observed.

E. Use-by Dating

Each vial is labeled with a use-by date appropriate to the formulation obtained from:

- Current literature
- Independent stability assay

F. Packaging

a. Compounded preparations are packaged in containers meeting USP standards.
b. Container used depends on the physical and chemical properties of the compounded preparation.

G. Dispensing

Product is dispensed by patient-specific prescription only. There must be a specific practitioner-patient-pharmacist relationship to dispense to an individual patient or facility.

H. Shipping

Medications are shipped overnight (usually via FedEx) in an appropriate container to ensure controlled temperatures and product integrity.

I. Licensing

NECC has undertaken a rigorous licensure process thus giving us the ability to legally dispense prescription medication in all 50 states.